Preventive Pharmacological Treatments for Migraine in Adults

Appendixes

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Appendix A. Literature Search

January, 2011
PubMed

#	Strings	N
8	Search "Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh] Limits: Humans, Meta-Analysis, English	97
7	Search "Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh] Limits: Humans, Randomized Controlled Trial, English	907

#	Strings	N
71	Search migraine NOT acute Limits: Humans, Randomized Controlled Trial, English	655
70	Search migraine Limits: Humans, Randomized Controlled Trial, English	1040
66	Search melatonin AND migraine	55
67	Search melatonin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	7
64	Search "Brain-Derived Neurotrophic Factor"[Mesh] AND migraine	6
63	Search "Brain-Derived Neurotrophic Factor"[Mesh] AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	1
62	Search "Brain-Derived Neurotrophic Factor"[Mesh] Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	94
58	Search Risperidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
57	Search Paliperidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
56	Search Methiothepin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
55	Search Metergoline AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
53	Search Lisuride AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	5
51	Search Bromocriptine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	4
50	Search Zotepine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
49	Search Ziprasidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
48	Search Trifluoperazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
47	Search Tenilapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
46	Search Sulpiride AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	1
45	Search Spiperone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
44	Search Sertindole AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
43	Search Olanzapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
42	Search Loxapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
41	Search Ketanserin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
40	Search Imipramine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
39	Search Fluperlapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
38	Search Fluphenazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
36	Search Cyproheptadine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	9
35	Search Clozapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
33	Search Clomipramine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	2
32	Search Aripiprazole AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
31	Search Amoxapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
29	Search Amitriptyline AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	34
28	Search Amitriptyline AND migraine Limits: Humans, English	150
27	Search 5-HT7 AND migraine Limits: Humans, English	12
24	Search 5-HT7 Limits: Humans, English	150
13	Search Quetiapine AND migraine Limits: Humans, English	5
21	Search "Antipsychotic Agents "[Pharmacological Action] AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	41

20	Search "Antipsychotic Agents "[Pharmacological Action] AND migraine Limits: Humans, English	206
19	Search "Antipsychotic Agents "[Pharmacological Action] Limits: Humans, English	51308
11	Search 5-HT2A AND migraine Limits: Humans, English	14
10	Search 5-HT2A antagonists AND migraine Limits: Humans, English	3
7	Search 5-HT2A antagonists Limits: Humans, English	394
5	Search Alpha-2 agonists AND migraine Limits: Humans, English	6
4	Search Alpha-2 agonists AND migraine	17

84	**Search telcagepant AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**4**
83	**Search olcegepant AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
82	**Search Arachidonic cascade modulators Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
80	**Search tonabersat) AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**6**
79	**Search dextromethorphan AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
78	**Search dextromethorphan AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
77	**Search loxapine AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
76	**Search prochlorperazine AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**8**
75	**Search prochlorperazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**20**

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#	Strings	N
15	Search Phenelzine AND migraine Limits: Humans, Journal Article, English	11
14	Search Bupropion AND migraine Limits: Humans, Journal Article, English	1
13	Search Imipramine AND migraine Limits: Humans, Journal Article, English	15
12	Search Imipramine AND headache Limits: Humans, Journal Article, English	60
11	Search Doxepin AND headache Limits: Humans, Journal Article, English	15
9	Search Desipramine AND headache Limits: Humans, Journal Article, English	13
10	Search Desipramine AND migraine Limits: Humans, Journal Article, English	1
7	Search Protriptyline AND headache Limits: Humans, Journal Article, English	4
6	Search Protriptyline AND migraine Limits: Humans, Journal Article, English	0

Updated search in Ovid; 1948 to November Week 3 2011

#	Searches	Results
1	exp migraine disorders/dt	5944
2	exp migraine disorders/pc	1669
3	ad.fs.	998247
4	2 and 3	286
5	1 or 4	6112
6	1 or 2	7065
7	exp "off-label use"/	519
8	off label.mp.	2412
9	7 or 8	2412
10	6 and 9	14
11	exp calcium channel blockers/	68976
12	exp antihypertensive agents/	216956
13	exp antidepressive agents/	113058
14	exp anticonvulsants/	111349
15	exp botulinum toxin type a/	4832
16	exp alzheimer disease/dt	8107

17	11 or 12 or 13 or 14 or 15 or 16	476372
18	6 and 17	1675
19	5 or 10 or 18	6489
20	limit 19 to (humans and yr="2000 -Current")	3195
21	limit 20 to updaterange="mesz(20111121020154-20111121091315]"	0

Ovid MEDLINE(R) 1946 to December Week 4 2011

#	Searches	Results
1	exp migraine disorders/dt	5882
2	exp migraine disorders/pc	1659
3	ad.fs.	975844
4	2 and 3	284
5	1 or 4	6048
6	1 or 2	6996
7	exp "off-label use"/	510
8	off label.mp.	2358
9	7 or 8	2358
10	6 and 9	13
11	exp calcium channel blockers/	67571
12	exp antihypertensive agents/	1420023
13	exp antidepressive agents/	110836
14	exp anticonvulsants/	1012405
15	exp botulinum toxin type a/	4648
16	exp alzheimer disease/dt	7829
17	11 or 12 or 13 or 14 or 15 or 16	2510533
18	6 and 17	1831
19	5 or 10 or 18	6431

Appendix B. Analytical Framework

PICOTS Framework

Population(s)

Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society[1] (see below for definitions).

Patient characteristics that can modify the effects of pharmacological treatments for preventing migraine attacks in children and adults:

- Age
- Sex
- Pregnancy
- Hormone-based birth control and hormone replacement
- The onset of menarche and menopause
- Race and ethnicity
- Socioeconomic status
- Education
- Family history
- Access to care, type of care, and residence in rural or urban areas
- Definition of migraine
- Presence of aura
- Headache frequency
- Prior treatments; overuse of drugs for acute migraine
- Obesity
- Nutritional and dietary factors, specifically caffeine
- Aerobic fitness
- Previous head injury
- Psychological factors and social/family support system
- Comorbidities (depression, bipolar disorder, anxiety, diabetes, hypertension, cardiovascular diseases, others)
- Concomitant medications for comorbid conditions

Interventions

Drugs approved by the FDA (such as propranolol, timolol, topiramate, and divalproex sodium) to prevent episodic migraine and to treat chronic migraine (such as Botox).

Off-label medications available in the United States and previously examined in clinical trials for preventing migraine.

Monotherapy.

Multidrug interventions.

Combined pharmacological with nonpharmacological modalities: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Comparators

Placebo.
Drug treatments (comparative effectiveness).
Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Outcomes

Patient-centered outcomes:
- Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review.
- Quality of life.
- Patient satisfaction.
- Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes.
- Emergency visits, loss of work days; treatment failure.

Intermediate outcomes:
- Number of headache days.
- Number of moderate to severe headache days.
- Improvement in associated symptoms.
- Use of drugs for acute migraine (prescribed or over-counter).
- Physician/healthcare professional (HCP) visits.

Harms:
- All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness).
- Treatment discontinuation due to adverse effects.
- Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).

Timing

6 months or more; optimally 12 months.
Any time of occurrence for the harms.

Setting

Outpatient settings

Definition of Terms

Migraine (as defined by the Headache Classification Subcommittee of the International Headache Society):[1]

Repeated attacks of headache lasting 4 to 72 hours in patients with a normal physical examination, no other reasonable cause for the headache, and:

At least two of the following features:
- Unilateral pain
- Throbbing pain

- Aggravation by movement
- Moderate or severe intensity

Plus at least one of the following features:

- Nausea/vomiting
- Photophobia and phonophobia

Episodic migraine as an indication for preventive treatment:

Five or more attacks a month[2]

Three or more attacks a month[2]

Definitions of chronic migraine (can be chronic from onset or transformed from episodic migraine):

FDA:

- Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.[3]

Revised International Headache Society criteria for chronic migraine:[1]

1.5.1. Chronic migraine

A. Headache (tension-type and/or migraine) on ≥15 days per month for at least 3 months

   * Characterization of a frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least 1 month.

B. Occurring in a patient who has had at least five attacks.

C. On ≥8 days per month for at least 3 months headache has fulfilled C.1 and/or C.2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura.

   1. Has at least two of a–d
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe pain intensity
      d. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) and at least one of (1) or (2):
         (1). Nausea and/or vomiting
         (2). Photophobia and phonophobia
   2. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above

D. No medication overuse† and not attributed to another causative disorder

   †Headache Classification Committee criteria for a medication overuse headache (A8.2)[1]

References

1. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID 16686915.
2. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
3. Administration USFaD. FDA News Release: FDA approves Botox to treat chronic migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.

Table 1. Pharmacological classes for migraine prevention

Drug, ATC Code*	Class of Drug
ANTIEPILEPTICS	
Topiramate, N03AX11	N03 ANTIEPILEPTICS N03AX Other antiepileptics
Lamotrigine, N03AX09	N03A ANTIEPILEPTICS
Levetiracetam, N03AX14	N03A ANTIEPILEPTICS
Pregabalin, N03AX16	N03A ANTIEPILEPTICS alpha2-delta agonist
Carbamazepine , N03AF01	N03A ANTIEPILEPTICS N03AF Carboxamide derivatives
Valproic acid, N03AG01	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, Gamma-aminobutyric acid (GABA) enhancer and analog
Vigabatrin, N03AG04	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, GABA transaminase inhibitor
Tiagabine, N03AG06	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, gamma aminobutyric acid (GABA) enhancer
Zonisamide, N03AX15	N03A ANTIEPILEPTICS N03AX Other antiepileptics
Valproate	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives
Divalproex	Gamma-aminobutyric acid (GABA) enhancer and analog
Gabapentin, N03AX12	N03A ANTIEPILEPTICS
Acetazolamide, S01EC01	S01EC, carbonic anhydrase inhibitor
ANTIDEPRESSANTS	
Nortriptyline , N06AA10	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Clomipramine, N06AA04	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Citalopram, N06AB04	N06A ANTIDEPRESSANTS N06AB selective serotonin reuptake inhibitors
Venlafaxine, N06AX16	N06A ANTIDEPRESSANTS N06AX Other antidepressants
Amitriptyline	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Mirtazapine, N06AX11	N06A ANTIDEPRESSANTS tricyclic antidepressants
BETA BLOCKERS	
Timolol, C07AA06	C07AA , Beta blocking agents, nonselective
Nadolol , C07AA12	C07AA Beta blocking agents, nonselective
Propranolol,C07AA05	C07AA Beta blocking agents, nonselective
Metoprolol,C07AB02	C07AB Beta blocking agents, selective
Atenolol, C07AB03	C07AB Beta blocking agents, selective
Bisoprolol,C07AB07	C07AB Beta blocking agents, selective
Acebutolol,C07AB04	C07AB Beta blocking agents, selective
Alprenolol, C07AA01 Oxprenolol, C07AA02 (discontinued in the FDA)	C07A BETA BLOCKING AGENTS C07AA Beta blocking agents, nonselective
Pindolol, C07AA03	C07AA Beta blocking agents, nonselective
ACE INHIBITORS	
Trandolapril, C09AA10	C09AA ACE inhibitors
Enalapril,C09AA02	C09AA ACE inhibitors
Captopril,C09AA01	C09AA ACE inhibitors
Lisinopril, C09AA03	C09AA ACE inhibitors
ANGIOTENSIN II ANTAGONISTS	
Telmisartan,C09CA07	C09CA Angiotensin II antagonists
Candesartan, C09CA06	C09CA Angiotensin II antagonists
CALCIUM CHANNEL ANTAGONIST	
Dotarizine	SELECTIVE CALCIUM CHANNEL ANTAGONIST; 5-HT receptors ANTAGONIST
Flunarizine, N07CA03; Sibelium	SELECTIVE CALCIUM CHANNEL ANTAGONISTN07C ANTIVERTIGO PREPARATIONS

Table 1. Pharmacological classes for migraine prevention (continued)

Drug, ATC Code*	Class of Drug
SELECTIVE CALCIUM CHANNEL BLOCKERS	
Nimodipine,C08CA06	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Verapamil,C08DA01	C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS C08DA Phenylalkylamine derivatives
Nicardipine,C08CA04	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Nifedipine,C08CA05	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
ANTIADRENERGICS	
Clonidine,C02AC01	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
Labetalol, C07AG01	C07AG , Alpha and beta blocking agents
Dixarit (clonidine, C02AC01) Guanfacine, C02AC02	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
ANTI-DEMENTIA	
Donepezil, N06DA02 Memantine, N06DX01	N06 PSYCHOANALEPTICS N06D ANTI-DEMENTIA DRUGS N-methyl-D-aspartate (NMDA) receptor inhibitor
ANTIPSYCHOTICS	
Aripiprazole,N05AX12	N05A ANTIPSYCHOTICS
Olanzapine,N05AH03	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Quetiapine,N05AH04	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Deanxit (Flupentixol, N05AF01)	N05A ANTIPSYCHOTICS N05AF Thioxanthene derivatives
Sulpiride, N05AL01 (antipsychotic)	N05A ANTIPSYCHOTICS N05AL Benzamides
Prochlorperazine, N05AB04	N05A ANTIPSYCHOTICS
DOPAMINERGIC AGENTS	
Amantadine, N04BB01	N04B DOPAMINERGIC AGENTS N04BB Adamantane derivatives N-methyl-D-aspartate (NMDA) receptor inhibitor
Dihydroergocryptine, N04BC03	N04B DOPAMINERGIC AGENTS N04BC Dopamine agonists
ERGOT ALKALOIDS	
Dihydroergotamine, N02CA01	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Lisuride, N02CA07 Ergotamine, N02CA02	N02C ANTIMIGRAINE PREPARATIONS N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Methysergide, N02CA04	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
MUSCLE RELAXANTS	
Botulinum Toxin Type A, M03AX01	M03A MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS M03AX Other muscle relaxants, peripherally acting agents
Tizanidine, M03BX02	M03B MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
SYSTEMIC DRUGS	
Montelukast, R03DC03	R03D OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES R03DC Leukotriene receptor antagonists

ATC code - The Anatomical Therapeutic Chemical classification

Table 2. Winbug Code for Bayesian network meta analysis

Outcome – reduction in monthly migraine by ≥50%

Treatments =11; trials=84

```
model {
for (i in 1:NS) {
s[i,1] <- 0
delta[i, t[i,1]] <- 0
mu[i] ~ dnorm(0, 0.0001)

for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
taud[i,t[i,k]] <- tau*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

d[1] <- 0
for (k in 2:NT) {
d[k] ~ dnorm(0,0.0001)
ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

sd~dunif(0.01,2)
tau<- 1/pow(sd,2)
var<- pow(sd,2)

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
for (k in 1:NT) {
for (c in 1:NT) {
lor[k,c] <- d[k] - d[c]
log(or[k,c]) <- lor[k,c]
    }
  }

  # difference of posterior probabilities
for (k in 2:NT) {
    PP[k] <- exp(mP+d[k])/(1+exp(mP+d[k])) - exp(mP)/(1+exp(mP))
  }

  # posterior probabilities
for (k in 1:NT) {
    pp[k] <- exp(mP+d[k])/(1+exp(mP+d[k]))
  }

  # ranking
mP<- mean(mu[1:27])         # Take average of mu[]

for (k in 1:NT) { logit(T[k]) <- mP + d[k] }     # T=prob of each trt
for (k in 1:NT) {
rk[k] <- NT + 1 - rank(T[],k)
```

```
best1[k] <- equals(rk[k],1)
best2[k] <- equals(rk[k],2)
best12[k] <- best1[k] + best2[k]
  }
}


#Init
#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0,0),
sd=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0)
)


#Data
list(NT=11, NS=84)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
8	12	0	12	NA	1	5	1	NA	2
27	45	30	45	NA	1	2	11	NA	2
37	58	41	67	NA	1	3	11	NA	2
20	22	21	22	NA	1	2	9	NA	2
16	40	15	40	NA	1	2	9	NA	2
12	20	6	20	NA	1	4	11	NA	2
13	23	8	23	NA	1	4	11	NA	2
1	14	2	14	NA	1	4	11	NA	2
99	178	78	169	NA	1	2	8	NA	2
32	66	34	69	NA	1	6	11	NA	2
14	48	24	54	NA	1	6	11	NA	2
6	18	6	14	NA	1	6	11	NA	2
3	15	1	14	NA	1	4	8	NA	2
40	135	61	135	NA	1	7	11	NA	2
14	28	3	28	NA	1	7	11	NA	2
10	31	8	31	NA	1	7	11	NA	2
15	22	14	22	NA	1	3	6	NA	2
5	44	18	47	NA	1	4	7	NA	2
15	36	17	36	NA	1	4	7	NA	2
16	32	13	27	NA	1	4	6	NA	2
0	17	5	17	NA	1	4	6	NA	2
125	270	141	275	NA	1	4	6	NA	2
8	34	12	35	NA	1	4	6	NA	2
24	48	31	46	NA	1	4	6	NA	2
20	24	21	25	NA	1	2	3	NA	2
24	37	25	37	NA	1	3	4	NA	2
5	19	2	21	NA	1	2	1	NA	2
12	34	3	36	NA	1	2	1	NA	2
37	58	12	57	NA	1	2	1	NA	2
58	112	8	36	NA	1	2	1	NA	2
188	386	93	372	NA	1	2	1	NA	2
177	384	86	372	NA	1	2	1	NA	2
55	140	25	73	NA	1	2	1	NA	2
10	14	1	14	NA	1	2	1	NA	2
62	165	47	163	NA	1	2	1	NA	2
72	165	89	163	NA	1	2	1	NA	2
7	32	0	27	NA	1	2	1	NA	2
45	75	44	74	NA	1	7	6	NA	2
50	144	11	49	62	144	2	1	4	3

19	44	2	15	NA	1	3	1	NA	2
17	43	6	43	NA	1	3	1	NA	2
50	123	32	116	NA	1	3	1	NA	2
5	8	0	11	NA	1	4	1	NA	2
34	83	17	83	NA	1	4	1	NA	2
5	13	9	15	NA	1	7	4	NA	2
62	144	11	49	NA	1	4	1	NA	2
48	96	12	48	44	96	4	1	7	3
13	25	3	13	14	25	4	1	7	3
14	60	0	60	NA	1	5	1	NA	2
26	60	1	60	NA	1	5	1	NA	2
16	48	11	47	NA	1	5	1	NA	2
10	30	0	30	NA	1	5	1	NA	2
3	11	1	13	NA	1	8	4	NA	2
7	24	11	25	NA	1	8	4	NA	2
10	54	12	54	NA	1	8	4	NA	2
5	29	0	29	NA	1	6	1	NA	2
20	72	17	71	NA	1	6	1	NA	2
8	29	2	29	NA	1	6	1	NA	2
10	17	4	18	NA	1	6	1	NA	2
3	28	0	28	NA	1	7	1	NA	2
29	77	16	77	NA	1	7	1	NA	2
6	24	0	8	NA	1	7	1	NA	2
8	24	0	24	NA	1	7	1	NA	2
2	14	0	14	NA	1	7	1	NA	2
10	34	4	37	NA	1	7	1	NA	2
25	47	10	47	NA	1	7	1	NA	2
6	16	1	16	NA	1	8	1	NA	2
16	37	7	36	NA	1	8	1	NA	2
9	21	0	19	NA	1	8	1	NA	2
24	59	24	65	NA	1	8	1	NA	2
26	55	18	61	NA	1	8	1	NA	2
8	26	9	27	NA	1	9	1	NA	2
26	98	5	45	NA	1	9	1	NA	2
28	85	31	85	NA	1	9	1	NA	2
18	23	12	22	NA	1	9	1	NA	2
26	48	5	48	NA	1	9	1	NA	2
28	60	20	60	38	60	9	1	2	3
112	184	112	200	NA	1	10	1	NA	2
10	33	0	33	NA	1	11	1	NA	2
8	30	4	30	NA	1	11	1	NA	2
23	93	18	84	NA	1	11	1	NA	2
17	40	1	40	NA	1	11	1	NA	2
10	35	10	34	NA	1	11	1	NA	2
14	36	7	32	NA	1	11	1	NA	2

END

Outcome = reduction in monthly migraine by ≥ 50%

Treatments =9; trials=79
Separate codes for the most effective beta-blockers

```
model {
for (i in 1:NS) {
s[i,1] <- 0
delta[i, t[i,1]] <- 0
```

```
mu[i] ~ dnorm(0, 0.0001)

for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
taud[i,t[i,k]] <- tau*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

d[1] <- 0
for (k in 2:NT) {
d[k] ~ dnorm(0,0.0001)
ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

sd~dunif(0.01,2)
tau<- 1/pow(sd,2)
var<- pow(sd,2)

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
for (k in 1:NT) {
for (c in 1:NT) {
lor[k,c] <- d[k] - d[c]
log(or[k,c]) <- lor[k,c]
    }
  }

  # difference of posterior probabilities
for (k in 2:NT) {
    PP[k] <- exp(mP+d[k])/(1+exp(mP+d[k])) - exp(mP)/(1+exp(mP))
  }

  # posterior probabilities
for (k in 1:NT) {
    pp[k] <- exp(mP+d[k])/(1+exp(mP+d[k]))
  }

  # ranking
mP<- mean(mu[1:27])         # Take average of mu[]

for (k in 1:NT) { logit(T[k]) <- mP + d[k] }     # T=prob of each trt
for (k in 1:NT) {
rk[k] <- NT + 1 - rank(T[],k)
best1[k] <- equals(rk[k],1)
best2[k] <- equals(rk[k],2)
best12[k] <- best1[k] + best2[k]
  }
}


#Init
#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0),
```

```
sd=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0)
)


#Data
list(NT=9, NS=79)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
50	144	11	49	62	144	7	1	2	3
48	96	12	48	44	96	2	1	3	3
13	25	3	13	14	25	2	1	3	3
7	24	11	25	10	27	6	2	9	3
24	48	31	46	NA	1	2	9	NA	2
12	20	6	20	NA	1	2	9	NA	2
13	23	8	23	NA	1	2	9	NA	2
125	270	141	275	NA	1	2	9	NA	2
8	34	12	35	NA	1	2	9	NA	2
0	17	5	17	NA	1	2	9	NA	2
1	14	2	14	NA	1	2	9	NA	2
16	32	13	27	NA	1	2	9	NA	2
45	75	44	74	NA	1	4	9	NA	2
14	28	3	28	NA	1	4	9	NA	2
10	31	8	31	NA	1	4	9	NA	2
39.96	135	61.02	135	NA	1	4	9	NA	2
3	15	1	14	NA	1	2	6	NA	2
5	44	18	47	NA	1	2	5	NA	2
15	22	14	22	NA	1	7	9	NA	2
15	36	17	36	NA	1	2	4	NA	2
27	45	30	45	NA	1	7	9	NA	2
37	58	41	67	NA	1	7	9	NA	2
7.98	14	8	16	NA	1	4	5	NA	2
11	125	12	125	NA	1	4	5	NA	2
34	83	17	83	NA	1	2	1	NA	2
99	178	78	169	NA	1	7	6	NA	2
5	8	0	11	NA	1	2	1	NA	2
2	14	0	14	NA	1	3	1	NA	2
25	47	10	47	NA	1	3	1	NA	2
29.26	77	16.17	77	NA	1	4	1	NA	2
5	13	9	15	NA	1	5	2	NA	2
10	34	4	37	NA	1	4	1	NA	2
10	54	12	54	NA	1	6	2	NA	2
3	28	0	28	NA	1	5	1	NA	2
6	24	0	8	NA	1	5	1	NA	2
3	11	1	13	NA	1	6	2	NA	2
8	24	0	24	NA	1	5	1	NA	2
26	55	18	61	NA	1	6	1	NA	2
6	16	1	16	NA	1	6	1	NA	2

24	37	25	37	NA	1	7	2	NA	2
9	21	0	19	NA	1	6	1	NA	2
24	59	24	65	NA	1	6	1	NA	2
16	37	7	36	NA	1	6	1	NA	2
26	48	5	48	NA	1	7	1	NA	2
17	43	6	43	NA	1	7	1	NA	2
19	44	2	15	NA	1	7	1	NA	2
26	98	5	45	NA	1	7	1	NA	2
5	19	2	21	NA	1	7	1	NA	2
8	26	9	27	NA	1	7	1	NA	2
50	123	32	116	NA	1	7	1	NA	2
12	34	3	36	NA	1	7	1	NA	2
10	14	1	14	NA	1	7	1	NA	2
37	58	12	57	NA	1	7	1	NA	2
188	386	93	372	NA	1	7	1	NA	2
55	140	25	73	NA	1	7	1	NA	2
28	60	20	60	NA	1	7	1	NA	2
7	32	0	27	NA	1	7	1	NA	2
177	384	86	372	NA	1	7	1	NA	2
72	165	89	163	NA	1	7	1	NA	2
28	85	31	85	NA	1	7	1	NA	2
62	165	47	163	NA	1	7	1	NA	2
18	23	12	22	NA	1	7	1	NA	2
58	112	8	36.38	NA	1	7	1	NA	2
14	60	0	60	NA	1	8	1	NA	2
26	60	1	60	NA	1	8	1	NA	2
8	12	0	12	NA	1	8	1	NA	2
16	48	11	47	NA	1	8	1	NA	2
10	17	4	18	NA	1	9	1	NA	2
14	36	7	32	NA	1	9	1	NA	2
10	35	10	34	NA	1	9	1	NA	2
23	93	18	84	NA	1	9	1	NA	2
112	184	112	200	NA	1	9	1	NA	2
10	33	0	33	NA	1	9	1	NA	2
8	29	2	29	NA	1	9	1	NA	2
20	72	17	71	NA	1	9	1	NA	2
8	30	4	30	NA	1	9	1	NA	2
5	29	0	29	NA	1	9	1	NA	2
17	40	1	40	NA	1	9	1	NA	2
10	30	0	30	NA	1	9	1	NA	2

END

Outcome- treatment discontinuation due to bothersome adverse effects
Number of treatments =10 Number of trials= 52

```
model {
for (i in 1:NS) {
s[i,1] <- 0
delta[i, t[i,1]] <- 0
mu[i] ~ dnorm(0, 0.0001)

for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
taud[i,t[i,k]] <- tau*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

d[1] <- 0
for (k in 2:NT) {
d[k] ~ dnorm(0,0.0001)
ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

sd~dunif(0.01,2)
tau<- 1/pow(sd,2)
var<- pow(sd,2)

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
for (k in 1:NT) {
for (c in 1:NT) {
lor[k,c] <- d[k] - d[c]
log(or[k,c]) <- lor[k,c]
    }
  }

  # difference of posterior probabilities
for (k in 2:NT) {
    PP[k] <- exp(mP+d[k])/(1+exp(mP+d[k])) - exp(mP)/(1+exp(mP))
  }

  # posterior probabilities
for (k in 1:NT) {
    pp[k] <- exp(mP+d[k])/(1+exp(mP+d[k]))
  }

  # ranking
mP<- mean(mu[1:27])         # Take average of mu[]

for (k in 1:NT) { logit(T[k]) <- mP + d[k] }     # T=prob of each trt
for (k in 1:NT) {
rk[k] <- NT + 1 - rank(T[],k)
best1[k] <- equals(rk[k],1)
best2[k] <- equals(rk[k],2)
best12[k] <- best1[k] + best2[k]
  }
}
```

```
#Init
#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0),
sd=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0, 0, 0)
)


#Data
list(NT=10, NS=52)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
3	60	3	60	3	60	9	1	2	3
3	44	9	49	3	48	8	10	4	3
1	13	0	15	NA	1	2	9	NA	2
3	67	2	58	NA	1	3	10	NA	2
2	24	4	28	NA	1	2	8	NA	2
35	178	38	169	NA	1	2	8	NA	2
1	66	6	69	NA	1	6	10	NA	2
0	48	4	54	NA	1	6	10	NA	2
2	18	1	14	NA	1	6	10	NA	2
4	44	2	47	NA	1	4	7	NA	2
0	31	4	31	NA	1	7	10	NA	2
3	48	5	46	NA	1	4	6	NA	2
18	270	19	275	NA	1	4	6	NA	2
3	32	2	27	NA	1	4	6	NA	2
1	75	10	74	NA	1	7	6	NA	2
18	63	0	63	NA	1	8	7	NA	2
4	37	1	37	NA	1	5	4	NA	2
6	34	0	36	NA	1	2	1	NA	2
24	128	3.80512	40.48	NA	1	2	1	NA	2
3	58	2	57	NA	1	2	1	NA	2
38	112	3.481566	36.38	NA	1	2	1	NA	2
9	30	6	20	NA	1	2	1	NA	2
21	140	4	73	NA	1	2	1	NA	2
24.57	117	4.5288	37.74	NA	1	2	1	NA	2
18	165	10	163	NA	1	2	1	NA	2
12	255	4	259	NA	1	2	1	NA	2
21	188	18	197	NA	1	2	1	NA	2
1	32	2	32	NA	1	3	1	NA	2
6	83	1	83	NA	1	4	1	NA	2
9	70	2	37	NA	1	5	1	NA	2
3	29	0	29	NA	1	8	4	NA	2

2	47	0	47	NA	1	7	1	NA	2
1	34	1	37	NA	1	7	1	NA	2
7	77	2.038725	38.25	NA	1	7	1	NA	2
3	28	0	28	NA	1	7	1	NA	2
0	72	3	72	NA	1	7	1	NA	2
5	55	2	61	NA	1	8	1	NA	2
0	31	1	34	NA	1	8	1	NA	2
4	27	4	26	NA	1	8	1	NA	2
2	59	1	65	NA	1	8	1	NA	2
23	194	13	197	NA	1	8	1	NA	2
3	29	2	30	NA	1	8	1	NA	2
1	48	0	48	NA	1	9	1	NA	2
4	43	2	43	NA	1	9	1	NA	2
1	19	3	40	NA	1	9	1	NA	2
16	98	4	45	NA	1	9	1	NA	2
9	26	2	27	NA	1	9	1	NA	2
10	123	10	116	NA	1	9	1	NA	2
8	85	4	85	NA	1	9	1	NA	2
2	23	1	22	NA	1	9	1	NA	2
1	74	2	74	NA	1	10	1	NA	2
12	75	5	75	NA	1	10	1	NA	2

END

Appendix C. Excluded Studies

Not eligible exposure[1-210211-460461-651]

1. Archambault ME. Do triptans increase the risk of thromboembolic stroke? JAAPA. 2006 Jul;19(7):57-8. PMID: 16869155.
2. Arora A, Arora S. Spontaneous splenic infarction associated with sumatriptan use. Journal of Headache & Pain. 2006 Sep;7(4):214-6. PMID: 16767537.
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4. Aurora SK, Barrodale PM, McDonald SA, et al. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. Headache. 2009 Jul;49(7):1001-4. PMID: 19438735.
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13. Bussone G, Manzoni GC, Cortelli P, et al. Efficacy and tolerability of sumatriptan in the treatment of multiple migraine attacks. Neurol Sci. 2000 Oct;21(5):272-8. PMID: 11286039.
14. Cabanas A, Rodriguez R, Rosado F, et al. Subcutaneous sumatriptan comparative study versus placebo in migraine attacks. Journal of The Neurological Sciences; 1997. p. S303.
15. Cabarrocas X, Esbri R, Peris F, et al. Long-term efficacy and safety of oral almotriptan: interim analysis of a 1-year open study. Headache. 2001 Jan;41(1):57-62. PMID: 11168604.
16. Cady R. Looking forward: the expanding utility of sumatriptan and naratriptan. Cephalalgia. 2001;21 Suppl 1:35-8. PMID: 11678821.
17. Cady R, Elkind A, Goldstein J, et al. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack versus dosing after the headache has become moderate or severe. Curr Med Res Opin. 2004 Sep;20(9):1465-72. PMID: 15383196.
18. Cady RC, Ryan R, Jhingran P, et al. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. Neurology; 1997. p. A121.
19. Caro G, Getsios D, Caro JJ, et al. Sumatriptan: economic evidence for its use in the treatment of migraine, the Canadian comparative economic analysis. Cephalalgia. 2001 Feb;21(1):12-9. PMID: 11298658.
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26. Connor HE. Building on the sumatriptan experience: the development of naratriptan. Cephalalgia. 2001;21 Suppl 1:32-4. PMID: 11678820.
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36. Diez-Tejedor FA. Assessment of response consistency to oral sumatriptan in migraine attacks. Journal of The Neurological Sciences; 1997.
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Appendix Table D1. Pharmacological groups and agents examined in randomized controlled trials for migraine prevention in adults

Pharmacological group of the drug in active group	Name of drug in active group/exposure level
ACE Inhibitors	Captopril
ACE Inhibitors	Lisinopril
Angiotensin II Antagonists	Candesartan
Angiotensin II Antagonists	Telmisartan
Anti-adrenergic	Catapresan
Anti-adrenergic	Clonidine
Anti-adrenergic	Guanfacine
Antidepressant	Amitriptyline
Antidepressant	Clomipramine
Antidepressant	Escitalopram
Antidepressant	Femoxetine
Antidepressant	Fluoxetine
Antidepressant	Fluvoxamine
Antidepressant	Mianserin
Antidepressant	Nortriptyline
Antidepressant	Tonabersat
Antidepressant	Venlafaxine
Anti-epileptic	Acetazolamide
Anti-epileptic	Carbamazepin
Anti-epileptic	Divalproex
Anti-epileptic	Gabapentin
Anti-epileptic	Lamotrigine
Anti-epileptic	Levetiracetam
Anti-epileptic	Oxcarbazepine
Anti-epileptic	Topiramate
Anti-epileptic	Valproate
Anti-epileptic	Vigabatrin
Anti-epileptic	Zonasamide
Beta-blocker	Atenolol
Beta-blocker	Metoprolol
Beta-blocker	Nadolol
Beta-blocker	Practolol
Beta-blocker	Propranolol
Beta-blocker	Timolol
Beta-blocker	Acebutolol
Beta-blocker	Alprenolol
Beta-blocker	Bisoprolol
Beta-blocker	Metaprolol
Beta-blocker	Nebivolol
Beta-blocker	Pindolol
Ergot alkaloid	Methysergide
Ergot alkaloid	Dihydroergotamine
Ergot alkaloid	Lisuride
Muscle relaxant	Tizanidine
NSAID	Acetylsalicyclic acid
NSAID	Fenoprofen
NSAID	Flurbiprofen
NSAID	Indomethacin
NSAID	Induprofen
NSAID	Ketoprofen
NSAID	Naproxen
NSAID	Tolfenamic Acid
Selective Calcium Channel Blockers	Nicardipine
Selective Calcium Channel Blockers	Nifedipine
Selective Calcium Channel Blockers	Nimodipine
Selective Calcium Channel Blockers	Verapamil
Systemic Drugs	Montelukast
Dopaminergic agent	Dihydroergocryptine
Magnesium	Magnesium
Antihistaminic	Cinnarizine

Appendix Table D2. Funding, ethical approval, and disclosure of conflict of interest in randomized controlled clinical trials of drugs for migraine prevention in adults

Drugs	Funded by grant	Funded by industry	Funding not reported	Combined funding	Clear reporting of ethical approval	Clear reporting of consent	No COI	COI not disclosed	Disclosed COI	Total
Approved antiepileptic, divalproex	0	3	0	0	2	2	0	0	3	3
Approved antiepileptic, topiramate	0	23	13	1	34	34	3	14	20	37
Approved antiepileptic, valproate	0	1	1	0	2	2	0	2	0	2
Beta-blockers, approved propranolol and off label	1	9	23	3	12	23	1	31	4	36
ACE inhibitors	0	1	1	0	1	2	0	1	1	2
Angiotensin II antagonists	0	1	1	0	1	1	0	1	1	2
Antiadrenergics, clonidine	0	5	8	0	2	10	0	13	0	13
Antidepressants	0	9	12	0	9	16	0	20	1	21
Antiepileptic, carbamazepin	0	1	0	0	0	0	0	1	0	1
Antiepileptic, gabapentin	0	0	3	0	1	2	0	3	0	3
Antiepileptic, lamotrigine	0	0	1	0	1	1	0	1	0	1
Antiepileptic, oxcarbazepine	0	1	0	0	1	1	0	0	1	1
Antiepileptic, vigabatrin	0	1	0	0	1	1	0	1	0	1
Carbonic anhydrase inhibitor, acetazolamide	0	1	0	0	1	1	0	1	0	1
Dihydroergocryptine	0	0	3	0	1	2	0	3	0	3
Ergot alkaloids	0	1	9	0	2	5	1	9	0	10
Magnesium	0	1	1	0	1	2	0	2	0	2
Muscle relaxants, tizanidine	0	1	0	0	0	1	0	1	0	1
NSAID, aspirin	0	0	1	0	0	1	0	1	0	1
Selective calcium channel blockers	1	6	5	0	2	8	0	10	2	12
Other off label drugs	1	1	3	0	1	2	0	5	0	5
Total	4	73	102	4	84	132	5	145	33	183

COI – conflict of interest

Appendix Table D3. Risk of bias in randomized controlled clinical trials of drugs for migraine prevention in adults

Drugs	Low	Moderate	Unclear	High	Total	% low
Approved antiepileptic, divalproex	2	1	0	0	3	66.7
Approved antiepileptic, topiramate	22	13	0	2	37	59.5
Approved antiepileptic, valproate	0	2	0	0	2	0.0
Beta-blockers, approved propranolol and off label	4	28	0	4	36	11.1
ACE inhibitors	1	1	0	0	2	50.0
Angiotensin II antagonists	2	0	0	0	2	100.0
Antiadrenergic, clonidine	4	8	1	0	13	30.8
Antidepressants	1	17	0	3	21	4.8
Antiepileptic, carbamazepin	0	1	0	0	1	0.0
Antiepileptic, gabapentin	0	3	0	0	3	0.0
Antiepileptic, lamotrigine	1	0	0	0	1	100.0
Antiepileptic, oxcarbazepine	1	0	0	0	1	100.0
Antiepileptic, vigabatrin	0	1	0	0	1	0.0
Carbonic anhydrase inhibitor, Acetazolamide	1	0	0	0	1	100.0
Dihydroergocryptine	0	2	0	1	3	0.0
Ergot alkaloids	2	8	0	0	10	20.0
Magnesium	1	0	0	1	2	50.0
Muscle relaxant, tizanidine	0	1	0	0	1	0.0
NSAID, aspirin	0	1	0	0	1	0.0
Selective Calcium channel blockers	4	5	1	2	12	33.3
Other off label drugs	2	3	0	0	5	40.0
Total	50	110	2	21	183	27.3

Appendix Table D4. Subject flow in randomized controlled clinical trials of drugs for migraine prevention in adults

Drugs	Number screened	Number of enrolled subjects	Total number randomized	Number analyzed	% excluded from analyses	% randomized/ screened	Number needed to screen to enroll one subject
Approved antiepileptic, divalproex	Not reported	197	174	171	1.7		
Approved antiepileptic, topiramate	416		385	382	0.8	92	1
Approved antiepileptic, valproate	Not reported	38	38	32	16.0		
Beta-blockers, approved propranolol and off label	384		118	102	13.7	31	3
ACE inhibitors	Not reported	290	123	113	7.8		
Muscle relaxant, tizanidine	Not reported	200	136	92	32.4		
Angiotensin II antagonists	63	36	36	34	6.9	57	2
Anti- adrenergic, clonidine	Not reported	57	56	49	11.7		
Antidepressant	342	93	84	59	29.7	25	4
Off label anti- epileptics, Carbamazepine		Not reported	Not reported	48			
Off label anti- epileptics, Gabapentin	201		84	61	27.7	42	2
Off label anti- epileptics, Lamotrigine	Not reported	110	77	77	0.0		
Off label anti- epileptics, Oxcarbazepine	324	170	170	170	0.0	52	2
Off label anti- epileptics, vigabatrin	Not reported	Not reported	23	15	34.8		
NSAID, aspirin	Not reported	45	45	38	15.6		
Carbonic anhydrase inhibitor, acetazolamide	Not reported	53	53	53	0.0		
Dihydroergocryptine	Not reported		57	30	47.7		
Ergot alkaloids	Not reported	129	112	106	5.4		
Magnesium	Not reported		47	42	10.8		
Selective calcium channel antagonists	Not reported		88	71	18.8		
Selective calcium channel blockers		1893	1892	1889	0.2		
Other off label drugs*	Not reported	50	50	44	12.0		

Other off label drugs* - antiadrenergic drugs

Appendix Table D5. Definition of migraine in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	Ad hoc committee on classification of headache	Chronic migraine	Common or classic migraine	International Headache Society	Not specified	Total
Approved antiepileptic, divalproex	0	0	0	3	0	3
Approved antiepileptic, topiramate	0	0	0	36	1	37
Approved antiepileptic, valproate	1	0	0	1	0	2
Beta-blockers, approved propranolol and off label	15	1	4	9	7	36
ACE inhibitors	1	0	0	1	0	2
Angiotensin II antagonists	1	0	0	1	0	2
Antiadrenergics, clonidine	6	0	0	2	5	13
Antidepressants	4	0	0	9	8	21
Antiepileptic, carbamazepine	0	0	0	0	1	1
Antiepileptic, gabapentin	0	0	1	2	0	3
Antiepileptic, lamotrigine	0	0	0	1	0	1
Antiepileptic, oxcarbazepine	0	0	0	1	0	1
Antiepileptic, vigabatrin	0	0	0	1	0	1
Carbonic anhydrase inhibitor, acetazolamide	0	0	0	1	0	1
Dihydroergocryptine	0	0	0	2	1	3
Ergot alkaloids	4	0	0	4	2	10
Magnesium	1	0	0	1	0	2
Muscle relaxants, tizanidine	0	0	0	1	0	1
NSAID, aspirin	1	0	0	0	0	1
Selective calcium channel blockers	4	0	0	4	4	12
Other off label drugs	2	0	1	1	1	5
Total	52	1	6	92	32	183

Appendix Table D6. Reporting of patient characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	Family history of migraine not reported	Hormone replacement therapy not reported	Socio-economic status not reported	Naïve to preventive drugs	Prior treatment status not reported	Total
Approved antiepileptic, divalproex	3	3	3	0	3	3
Approved antiepileptic, topiramate	37	37	37	5	32	37
Approved antiepileptic, valproate	2	2	2	0	2	2
Beta-blockers, approved propranolol and off label	30	36	35	2	34	36
ACE inhibitors	2	2	2	0	2	2
Angiotensin II antagonists	2	2	2	0	2	2
Antiadrenergic, clonidine	10	13	13	2	11	13
Antidepressants	19	21	21	3	18	21
Antiepileptic, carbamazepine	0	1	1	0	1	1
Antiepileptic, gabapentin	2	3	3	0	3	3
Antiepileptic, lamotrigine	1	1	1	0	1	1
Antiepileptic, oxcarbazepine	1	1	1	0	1	1
Antiepileptic, vigabatrin	1	1	1	1	0	1
Carbonic anhydrase inhibitor, acetazolamide	1	1	1	0	1	1
Dihydroergocryptine	3	3	3	0	3	3
Ergot alkaloids	8	10	10	1	9	10
Magnesium	2	2	2	1	1	2
Muscle relaxant, tizanidine	1	1	1	0	1	1
NSAID, aspirin	1	1	1	0	1	1
Selective calcium channel blockers	9	11	12	0	12	12
Other off label drugs*	4	5	5	1	4	5

Other off label drugs*- antiadrenergic drugs

Appendix Table D7. Age of participants in randomized controlled clinical trials of drugs for migraine prevention in adults

Drugs	Mean	Minimum	Maximum	# of RCTs that reported age	Total	% reported
Total	37.9	28.6	53.2			
Approved antiepileptic divalproex	42.3	40.5	45.6	3	3	100
Approved antiepileptic, topiramate	39.1	29.4	46.0	34	37	92
Approved antiepileptic, valproate	40.0	34.0	46.0	2	2	100
Beta-blockers, approved propranolol and off label	37.9	28.6	43.5	27	36	75
ACE inhibitors	40.0	40.0	40.0	1	2	50
Angiotensin II antagonists	45.0	41.0	49.0	2	2	100
Anti-adrenergic, clonidine	36.8	32.0	48.0	10	13	77
Antidepressants	36.2	31.0	40.6	17	21	81
Antiepileptic, carbamazepine	Not reported	Not reported	Not reported		1	0
Antiepileptic, gabapentin	41.3	39.6	43.0	2	3	67
Antiepileptic, lamotrigine	37.2	37.2	37.2	1	1	100
Antiepileptic, oxcarbazepine	40.5	40.5	40.5	1	1	100
Antiepileptic, vigabatrin	43.6	43.6	43.6	1	1	100
NSAID, aspirin	39.6	39.6	39.6	1	1	100
Carbonic anhydrase inhibitor, acetazolamide	39.2	39.2	39.2	1	1	100
Dihydroergocryptine	34.3	33.9	34.6	2	3	67
Ergot alkaloids	38.6	30.0	47.0	8	10	80
Magnesium	41.0	41.0	41.0	1	2	50
Muscle relaxant, tizanidine	40.3	40.3	40.3	1	1	100
Selective calcium channel blockers	37.4	29.8	53.2	10	12	83
Other off label drugs*	39.3	33.2	45.4	4	5	80

Other off label drugs* - antiadrenergic drugs

Appendix Table D8. Proportion of women in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	Mean	Minimum	Maximum	# of RCTs that reported age	Total	% reported
Total	65.3	0.0	97.5			
Approved antiepileptic, divalproex	81.9	77.6	89.0	3	3	100
Approved antiepileptic, topiramate	79.8	10.9	97.5	35	37	95
Approved antiepileptic, valproate	82.7	79.3	86.0	2	2	100
Beta-blockers, approved propranolol and off label	78.2	52.0	94.5	32	36	89
ACE inhibitors	44.4	0.7	88.0	2	2	100
Angiotensin II antagonists	40.8	0.6	81.0	2	2	100
Anti-adrenergic, clonidine	7.5	0.7	81.0	12	13	92
Antidepressants	80.7	63.5	92.3	19	21	90
Antiepileptic, carbamazepine	68.8	68.8	68.8	1	1	100
Antiepileptic, gabapentin	74.7	52.4	88.9	3	3	100
Antiepileptic, lamotrigine	81.8	81.8	81.8	1	1	100
Antiepileptic, oxcarbazepine	84.7	84.7	84.7	1	1	100
Antiepileptic, vigabatrin	73.9	73.9	73.9	1	1	100
NSAID, aspirin	0.7	0.7	0.7	1	1	100
Carbonic anhydrase inhibitor, acetazolamide	75.5	75.5	75.5	1	1	100
Dihydroergocryptine	74.4	71.6	76.7	3	3	100
Ergot alkaloids	62.4	0.9	83.3	9	10	90
Magnesium	93.0	93.0	93.0	1	2	50
Muscle relaxant, tizanidine	79.0	79.0	79.0	1	1	100
Selective calcium channel blockers	25.4	0.0	86.0	12	12	100
Other off label drugs*	0.8	0.7	0.8	5	5	100

Other off label drugs* - antiadrenergic drugs

Appendix Table D9. Baseline monthly migraine frequency in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	Mean	Minimum	Maximum	# of RCTs that reported age	Total	% reported
Total	5.7	2.0	26.6			
Approved antiepileptic, divalproex	5.8	5.8	5.8	1	3	33
Approved antiepileptic, topiramate	7.4	4.1	26.6	27	37	73
Approved antiepileptic, valproate	5.8	5.0	6.6	2	2	100
Beta-blockers, approved propranolol and off label	5.1	2.9	7.2	23	36	64
ACE inhibitors	5.1	5.1	5.1	1	2	50
Angiotensin II antagonists	Not reported	Not reported.	Not reported		1	0
Anti-adrenergic, clonidine	Not reported	Not reported.	Not reported		2	0
Antidepressants	4.0	3.9	4.0	2	13	15
Antiepileptic, carbamazepine	Not reported	Not reported.	Not reported		21	0
Antiepileptic, gabapentin	3.0	3.0	3.0	1	1	100
Antiepileptic, lamotrigine	5.0	4.9	5.0	3	3	100
Antiepileptic, oxcarbazepine	4.0	4.0	4.0	1	1	100
Antiepileptic, vigabatrin	6.0	6.0	6.0	1	1	100
NSAID, aspirin	2.0	2.0	2.0	1	1	100
Carbonic anhydrase inhibitor, acetazolamide	Not reported	Not reported.	Not reported		1	0
Dihydroergocryptine	5.0	5.0	5.0	1	1	100
Ergot alkaloids	5.8	5.5	6.0	3	3	100
Magnesium	4.7	3.3	8.5	6	10	60
Muscle relaxant, tizanidine	Not reported	Not reported.	Not reported		2	0
Selective calcium channel blockers	6.1	4.0	10.0	4	12	33
Other off label drugs*	4.6	3.4	5.8	2	5	40

Other off label drugs* - antiadrenergic drugs

Appendix Table D10. Percentage of loss of followup in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	Mean	Minimum	Maximum	# of RCTs that reported age	Total	% reported
Total	13.0	0.0	48.3			
Approved antiepileptic, divalproex	1.2	0.0	2.9	3	3	100
Approved antiepileptic, topiramate	Not reported	Not reported.	Not reported		37	0
Approved antiepileptic, valproate	3.5	0.0	7.0	2	2	100
Beta-blockers, approved propranolol and off label	12.3	0.0	37.5	36	36	100
ACE inhibitors	7.1	2.2	12.0	2	2	100
Angiotensin II antagonists	Not reported	Not reported.	Not reported		2	0
Anti-adrenergic, clonidine	24.5	13.0	36.0	2	13	15
Antidepressants	21.8	0.0	48.0	20	21	95
Antiepileptic, carbamazepine	6.3	6.3	6.3	1	1	100
Antiepileptic, gabapentin	2.0	0.0	6.1	3	3	100
Antiepileptic, lamotrigine	0.0	0.0	0.0	1	1	100
Antiepileptic, oxcarbazepine	3.5	3.5	3.5	1	1	100
Antiepileptic, vigabatrin	0.0	0.0	0.0	1	1	100
NSAID, aspirin	Not reported	Not reported.	Not reported		1	0
Carbonic anhydrase inhibitor, acetazolamide	0.0	0.0	0.0	1	1	100
Dihydroergocryptine	Not reported	Not reported.	Not reported		3	0
Ergot alkaloids	10.9	0.0	32.4	10	10	100
Magnesium	11.0	11.0	11.0	1	2	50
Muscle relaxant, tizanidine	Not reported	Not reported.	Not reported		1	0
Selective calcium channel blockers	11.3	0.0	20.0	5	12	42
Other off label drugs*	7.0	7.0	7.0	1	5	20

Other off label drugs* - antiadrenergic drugs

Appendix Table D11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% Loss of followup	ACE inhibitors	Acetazolamide	7.1	-22.0	36.2
% Loss of followup	ACE inhibitors	Antidepressant	-14.7	-32.3	3.0
% Loss of followup	ACE inhibitors	Ca channel antagonists	-4.2	-24.2	15.7
% Loss of followup	ACE inhibitors	Carbamazepine	0.8	-28.3	29.9
% Loss of followup	ACE inhibitors	Clonidine	-17.4	-41.2	6.4
% Loss of followup	ACE inhibitors	Divalproex	5.9	-15.8	27.6
% Loss of followup	ACE inhibitors	Ergot alkaloids	-3.8	-22.2	14.7
% Loss of followup	ACE inhibitors	Gabapentin	5.1	-16.7	26.8
% Loss of followup	ACE inhibitors	Lamotrigine	7.1	-22.0	36.2
% Loss of followup	ACE inhibitors	Magnesium	-3.9	-33.0	25.2
% Loss of followup	ACE inhibitors	Other* off label drugs	0.1	-29.0	29.2
% Loss of followup	ACE inhibitors	Oxcarbazepine	3.6	-25.5	32.7
% Loss of followup	ACE inhibitors	Propranolol	-5.2	-22.5	12.1
% Loss of followup	ACE inhibitors	Valproate	3.6	-20.2	27.4
% Loss of followup	ACE inhibitors	Vigabatrin	7.1	-22.0	36.2
% Loss of followup	Acetazolamide	Antidepressant	-21.8	-46.2	2.6
% Loss of followup	Acetazolamide	Ca channel antagonists	-11.3	-37.4	14.7
% Loss of followup	Acetazolamide	Carbamazepine	-6.3	-40.0	27.4
% Loss of followup	Acetazolamide	Clonidine	-24.5	-53.6	4.6
% Loss of followup	Acetazolamide	Divalproex	-1.2	-28.7	26.3
% Loss of followup	Acetazolamide	Ergot alkaloids	-10.9	-35.8	14.1
% Loss of followup	Acetazolamide	Gabapentin	-2.0	-29.5	25.4
% Loss of followup	Acetazolamide	Lamotrigine	0.0	-33.7	33.7
% Loss of followup	Acetazolamide	Magnesium	-11.0	-44.7	22.7
% Loss of followup	Acetazolamide	Other* off label drugs	-7.0	-40.7	26.7
% Loss of followup	Acetazolamide	Oxcarbazepine	-3.5	-37.2	30.2
% Loss of followup	Acetazolamide	Propranolol	-12.3	-36.4	11.8
% Loss of followup	Acetazolamide	Valproate	-3.5	-32.6	25.6
% Loss of followup	Acetazolamide	Vigabatrin	0.0	-33.7	33.7
% Loss of followup	Antidepressant	Ca channel antagonists	10.4	-1.5	22.3
% Loss of followup	Antidepressant	Carbamazepine	15.5	-8.9	39.9
% Loss of followup	Antidepressant	Clonidine	-2.7	-20.4	14.9
% Loss of followup	**Antidepressant**	**Divalproex**	**20.5**	**5.8**	**35.3**
% Loss of followup	**Antidepressant**	**Ergot alkaloids**	**10.9**	**1.7**	**20.1**
% Loss of followup	**Antidepressant**	**Gabapentin**	**19.7**	**5.0**	**34.5**
% Loss of followup	Antidepressant	Lamotrigine	21.8	-2.6	46.2
% Loss of followup	Antidepressant	Magnesium	10.8	-13.6	35.2
% Loss of followup	Antidepressant	OOther* off label drugs	14.8	-9.6	39.2
% Loss of followup	Antidepressant	Oxcarbazepine	18.3	-6.1	42.7

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% Loss of followup	**Antidepressant**	**Propranolol**	**9.5**	**2.8**	**16.1**
% Loss of followup	**Antidepressant**	**Valproate**	**18.3**	**0.6**	**35.9**
% Loss of followup	Antidepressant	Vigabatrin	21.8	-2.6	46.2
% Loss of followup	Ca channel antagonists	Carbamazepine	5.0	-21.0	31.1
% Loss of followup	Ca channel antagonists	Clonidine	-13.2	-33.1	6.8
% Loss of followup	Ca channel antagonists	Divalproex	10.1	-7.3	27.5
% Loss of followup	Ca channel antagonists	Ergot alkaloids	0.5	-12.5	13.5
% Loss of followup	Ca channel antagonists	Gabapentin	9.3	-8.1	26.7
% Loss of followup	Ca channel antagonists	Lamotrigine	11.3	-14.7	37.4
% Loss of followup	Ca channel antagonists	Magnesium	0.3	-25.7	26.4
% Loss of followup	Ca channel antagonists	Other* off label drugs	4.3	-21.7	30.4
% Loss of followup	Ca channel antagonists	Oxcarbazepine	7.8	-18.2	33.9
% Loss of followup	Ca channel antagonists	Propranolol	-1.0	-12.3	10.4
% Loss of followup	Ca channel antagonists	Valproate	7.8	-12.1	27.8
% Loss of followup	Ca channel antagonists	Vigabatrin	11.3	-14.7	37.4
% Loss of followup	Carbamazepine	Clonidine	-18.2	-47.3	10.9
% Loss of followup	Carbamazepine	Divalproex	5.1	-22.4	32.6
% Loss of followup	Carbamazepine	Ergot alkaloids	-4.6	-29.5	20.4
% Loss of followup	Carbamazepine	Gabapentin	4.3	-23.2	31.7
% Loss of followup	Carbamazepine	Lamotrigine	6.3	-27.4	40.0
% Loss of followup	Carbamazepine	Magnesium	-4.7	-38.4	29.0
% Loss of followup	Carbamazepine	Other* off label drugs	-0.7	-34.4	33.0
% Loss of followup	Carbamazepine	Oxcarbazepine	2.8	-30.9	36.5
% Loss of followup	Carbamazepine	Propranolol	-6.0	-30.1	18.1
% Loss of followup	Carbamazepine	Valproate	2.8	-26.3	31.9
% Loss of followup	Carbamazepine	Vigabatrin	6.3	-27.4	40.0
% Loss of followup	Clonidine	Other* off label drugs	17.5	-11.6	46.6
% Loss of followup	Clonidine	Vigabatrin	24.5	-4.6	53.6
% Loss of followup	**Divalproex**	**Clonidine**	**-23.3**	**-45.0**	**-1.6**
% Loss of followup	Divalproex	Ergot alkaloids	-9.6	-25.3	6.0
% Loss of followup	Divalproex	Gabapentin	-0.8	-20.2	18.6
% Loss of followup	Divalproex	Lamotrigine	1.2	-26.3	28.7
% Loss of followup	Divalproex	Magnesium	-9.8	-37.3	17.7
% Loss of followup	Divalproex	Other* off label drugs	-5.8	-33.3	21.7
% Loss of followup	Divalproex	Oxcarbazepine	-2.3	-29.8	25.2
% Loss of followup	Divalproex	Propranolol	-11.1	-25.4	3.2
% Loss of followup	Divalproex	Valproate	-2.3	-24.0	19.4
% Loss of followup	Divalproex	Vigabatrin	1.2	-26.3	28.7
% Loss of followup	Ergot alkaloids	Clonidine	-13.7	-32.1	4.8
% Loss of followup	Ergot alkaloids	Gabapentin	8.8	-6.8	24.5

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% Loss of followup	Ergot alkaloids	Lamotrigine	10.9	-14.1	35.8
% Loss of followup	Ergot alkaloids	Magnesium	-0.2	-25.1	24.8
% Loss of followup	Ergot alkaloids	Other* off label drugs	3.9	-21.1	28.8
% Loss of followup	Ergot alkaloids	Oxcarbazepine	7.4	-17.6	32.3
% Loss of followup	Ergot alkaloids	Propranolol	-1.5	-10.0	7.1
% Loss of followup	Ergot alkaloids	Valproate	7.4	-11.1	25.8
% Loss of followup	Ergot alkaloids	Vigabatrin	10.9	-14.1	35.8
% Loss of followup	**Gabapentin**	**Clonidine**	**-22.5**	**-44.2**	**-0.7**
% Loss of followup	Gabapentin	Lamotrigine	2.0	-25.4	29.5
% Loss of followup	Gabapentin	Magnesium	-9.0	-36.4	18.5
% Loss of followup	Gabapentin	Other* off label drugs	-5.0	-32.4	22.5
% Loss of followup	Gabapentin	Oxcarbazepine	-1.5	-28.9	26.0
% Loss of followup	Gabapentin	Propranolol	-10.3	-24.6	4.0
% Loss of followup	Gabapentin	Valproate	-1.5	-23.2	20.3
% Loss of followup	Gabapentin	Vigabatrin	2.0	-25.4	29.5
% Loss of followup	Lamotrigine	Clonidine	-24.5	-53.6	4.6
% Loss of followup	Lamotrigine	Magnesium	-11.0	-44.7	22.7
% Loss of followup	Lamotrigine	Other* off label drugs	-7.0	-40.7	26.7
% Loss of followup	Lamotrigine	Oxcarbazepine	-3.5	-37.2	30.2
% Loss of followup	Lamotrigine	Propranolol	-12.3	-36.4	11.8
% Loss of followup	Lamotrigine	Valproate	-3.5	-32.6	25.6
% Loss of followup	Lamotrigine	Vigabatrin	0.0	-33.7	33.7
% Loss of followup	Magnesium	Clonidine	-13.5	-42.6	15.6
% Loss of followup	Magnesium	Other* off label drugs	4.0	-29.7	37.7
% Loss of followup	Magnesium	Oxcarbazepine	7.5	-26.2	41.2
% Loss of followup	Magnesium	Propranolol	-1.3	-25.4	22.8
% Loss of followup	Magnesium	Valproate	7.5	-21.6	36.6
% Loss of followup	Magnesium	Vigabatrin	11.0	-22.7	44.7
% Loss of followup	Other off label drugs	Vigabatrin	7.0	-26.7	40.7
% Loss of followup	Oxcarbazepine	Clonidine	-21.0	-50.1	8.1
% Loss of followup	Oxcarbazepine	Other* off label drugs	-3.5	-37.2	30.2
% Loss of followup	Oxcarbazepine	Propranolol	-8.8	-32.9	15.3
% Loss of followup	Oxcarbazepine	Valproate	0.0	-29.1	29.1
% Loss of followup	Oxcarbazepine	Vigabatrin	3.5	-30.2	37.2
% Loss of followup	Propranolol	Clonidine	-12.2	-29.5	5.1
% Loss of followup	Propranolol	Other* off label drugs	5.3	-18.8	29.4
% Loss of followup	Propranolol	Valproate	8.8	-8.5	26.1
% Loss of followup	Propranolol	Vigabatrin	12.3	-11.8	36.4
% Loss of followup	Valproate	Clonidine	-21.0	-44.8	2.8
% Loss of followup	Valproate	Other* off label drugs	-3.5	-32.6	25.6

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% Loss of followup	Valproate	Vigabatrin	3.5	-25.6	32.6
% with good adherence	Angiotensin receptor blockers	Antidepressant	-2.0	-96.0	92.0
% with good adherence	Angiotensin receptor blockers	Ca channel antagonist	-8.0	-102.0	86.0
% with good adherence	Angiotensin receptor blockers	Gabapentin	0.7	-93.3	94.7
% with good adherence	Angiotensin receptor blockers	Oxcarbazepine	12.0	-82.0	106.0
% with good adherence	Angiotensin receptor blockers	Propranolol	-1.7	-83.1	79.7
% with good adherence	Angiotensin receptor blockers	Topiramate	7.0	-87.0	101.0
% with good adherence	Antidepressant	Ca channel antagonist	-6.0	-100.0	88.0
% with good adherence	Antidepressant	Gabapentin	2.7	-91.3	96.7
% with good adherence	Antidepressant	Oxcarbazepine	14.0	-80.0	108.0
% with good adherence	Antidepressant	Propranolol	0.3	-81.1	81.7
% with good adherence	Antidepressant	Topiramate	9.0	-85.0	103.0
% with good adherence	Ca channel antagonist	Gabapentin	8.7	-85.3	102.7
% with good adherence	Ca channel antagonist	Oxcarbazepine	20.0	-74.0	114.0
% with good adherence	Ca channel antagonist	Propranolol	6.3	-75.1	87.7
% with good adherence	Ca channel antagonist	Topiramate	15.0	-79.0	109.0
% with good adherence	Gabapentin	Oxcarbazepine	11.3	-82.7	105.3
% with good adherence	Gabapentin	Propranolol	-2.4	-83.8	79.0
% with good adherence	Gabapentin	Topiramate	6.3	-87.7	100.3
% with good adherence	Oxcarbazepine	Propranolol	-13.7	-95.1	67.7
% with good adherence	Oxcarbazepine	Topiramate	-5.0	-99.0	89.0
% with good adherence	Propranolol	Topiramate	8.7	-72.7	90.1
% women	ACE inhibitors	Acetazolamide	-31.1	-75.1	12.8
% women	ACE inhibitors	Angiotensin receptor blockers	3.6	-32.3	39.4
% women	**ACE inhibitors**	**Antidepressant**	**-36.4**	**-63.1**	**-9.7**
% women	ACE inhibitors	Aspirin	43.7	-0.3	87.6
% women	ACE inhibitors	Ca channel antagonists	18.9	-8.5	46.3
% women	ACE inhibitors	Carbamazepine	-24.4	-68.4	19.5
% women	**ACE inhibitors**	**Clonidine**	**36.9**	**9.5**	**64.3**
% women	ACE inhibitors	Dihydroergocryptine	-30.1	-62.8	2.7
% women	**ACE inhibitors**	**Divalproex**	**-37.5**	**-70.3**	**-4.8**
% women	ACE inhibitors	Ergot alkaloids	-18.0	-46.1	10.0
% women	ACE inhibitors	Gabapentin	-30.3	-63.1	2.4
% women	ACE inhibitors	Lamotrigine	-37.4	-81.4	6.5
% women	**ACE inhibitors**	**Magnesium**	**-48.6**	**-92.6**	**-4.7**
% women	**ACE inhibitors**	**Other****	**43.6**	**13.6**	**73.6**
% women	ACE inhibitors	Oxcarbazepine	-40.3	-84.3	3.6
% women	**ACE inhibitors**	**Propranolol**	**-33.9**	**-60.0**	**-7.7**
% women	ACE inhibitors	Tizanidine	-34.6	-78.6	9.3
% women	**ACE inhibitors**	**Topiramate**	**-35.5**	**-61.5**	**-9.4**

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% women	**ACE inhibitors**	**Valproate**	**-38.3**	**-74.2**	**-2.4**
% women	ACE inhibitors	Vigabatrin	-29.5	-73.5	14.4
% women	Acetazolamide	Antidepressant	-5.2	-42.1	31.6
% women	**Acetazolamide**	**Aspirin**	**74.8**	**24.1**	**125.6**
% women	**Acetazolamide**	**Ca channel antagonists**	**50.1**	**12.7**	**87.4**
% women	Acetazolamide	Carbamazepine	6.7	-44.0	57.4
% women	**Acetazolamide**	**Clonidine**	**68.0**	**30.7**	**105.4**
% women	Acetazolamide	Dihydroergocryptine	1.1	-40.3	42.5
% women	Acetazolamide	Divalproex	-6.4	-47.8	35.1
% women	Acetazolamide	Ergot alkaloids	13.1	-24.7	50.9
% women	Acetazolamide	Gabapentin	0.8	-40.6	42.2
% women	Acetazolamide	Lamotrigine	-6.3	-57.0	44.4
% women	Acetazolamide	Magnesium	-17.5	-68.2	33.2
% women	**Acetazolamide**	**Other****	**74.7**	**35.4**	**114.0**
% women	Acetazolamide	Oxcarbazepine	-9.2	-59.9	41.5
% women	Acetazolamide	Propranolol	-2.7	-39.1	33.7
% women	Acetazolamide	Tizanidine	-3.5	-54.2	47.2
% women	Acetazolamide	Topiramate	-4.3	-40.7	32.1
% women	Acetazolamide	Valproate	-7.2	-51.1	36.8
% women	Acetazolamide	Vigabatrin	1.6	-49.1	52.3
% women	Angiotensin receptor blockers	Acetazolamide	-34.7	-78.7	9.2
% women	**Angiotensin receptor blockers**	**Antidepressant**	**-40.0**	**-66.6**	**-13.3**
% women	Angiotensin receptor blockers	Aspirin	40.1	-3.8	84.0
% women	Angiotensin receptor blockers	Ca channel antagonists	15.3	-12.1	42.7
% women	Angiotensin receptor blockers	Carbamazepine	-28.0	-72.0	15.9
% women	**Angiotensin receptor blockers**	**Clonidine**	**33.3**	**5.9**	**60.7**
% women	**Angiotensin receptor blockers**	**Dihydroergocryptine**	**-33.6**	**-66.4**	**-0.9**
% women	**Angiotensin receptor blockers**	**Divalproex**	**-41.1**	**-73.8**	**-8.3**
% women	Angiotensin receptor blockers	Ergot alkaloids	-21.6	-49.6	6.5
% women	**Angiotensin receptor blockers**	**Gabapentin**	**-33.9**	**-66.7**	**-1.2**
% women	Angiotensin receptor blockers	Lamotrigine	-41.0	-85.0	2.9
% women	**Angiotensin receptor blockers**	**Magnesium**	**-52.2**	**-96.2**	**-8.3**
% women	**Angiotensin receptor blockers**	**Other***	**40.0**	**10.0**	**70.0**
% women	Angiotensin receptor blockers	Oxcarbazepine	-43.9	-87.9	0.0

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% women	**Angiotensin receptor blockers**	**Propranolol**	**-37.4**	**-63.6**	**-11.3**
% women	Angiotensin receptor blockers	Tizanidine	-38.2	-82.2	5.7
% women	**Angiotensin receptor blockers**	**Topiramate**	**-39.0**	**-65.1**	**-12.9**
% women	**Angiotensin receptor blockers**	**Valproate**	**-41.9**	**-77.7**	**-6.0**
% women	Angiotensin receptor blockers	Vigabatrin	-33.1	-77.1	10.8
% women	**Antidepressant**	**Aspirin**	**80.1**	**43.2**	**116.9**
% women	**Antidepressant**	**Ca channel antagonists**	**55.3**	**42.1**	**68.5**
% women	Antidepressant	Carbamazepine	11.9	-24.9	48.8
% women	**Antidepressant**	**Clonidine**	**73.3**	**60.0**	**86.5**
% women	Antidepressant	Dihydroergocryptine	6.3	-16.0	28.6
% women	Antidepressant	Divalproex	-1.1	-23.4	21.2
% women	**Antidepressant**	**Ergot alkaloids**	**18.4**	**3.8**	**32.9**
% women	Antidepressant	Gabapentin	6.0	-16.2	28.3
% women	Antidepressant	Lamotrigine	-1.1	-37.9	35.8
% women	Antidepressant	Magnesium	-12.3	-49.1	24.6
% women	**Antidepressant**	**Other***	**80.0**	**61.9**	**98.0**
% women	Antidepressant	Oxcarbazepine	-4.0	-40.8	32.9
% women	Antidepressant	Propranolol	2.5	-7.9	12.9
% women	Antidepressant	Tizanidine	1.7	-35.1	38.6
% women	Antidepressant	Topiramate	0.9	-9.3	11.2
% women	Antidepressant	Valproate	-1.9	-28.6	24.8
% women	Antidepressant	Vigabatrin	6.8	-30.0	43.7
% women	Aspirin	Clonidine	-6.8	-44.1	30.5
% women	**Aspirin**	**Dihydroergocryptine**	**-73.7**	**-115.2**	**-32.3**
% women	Aspirin	Other*	-0.1	-39.4	39.2
% women	**Aspirin**	**Tizanidine**	**-78.3**	**-129.1**	**-27.6**
% women	**Aspirin**	**Vigabatrin**	**-73.2**	**-124.0**	**-22.5**
% women	Ca channel antagonists	Aspirin	24.8	-12.6	62.1
% women	**Ca channel antagonists**	**Carbamazepine**	**-43.4**	**-80.7**	**-6.0**
% women	**Ca channel antagonists**	**Clonidine**	**18.0**	**3.3**	**32.6**
% women	**Ca channel antagonists**	**Dihydroergocryptine**	**-49.0**	**-72.1**	**-25.8**
% women	**Ca channel antagonists**	**Divalproex**	**-56.4**	**-79.6**	**-33.3**
% women	**Ca channel antagonists**	**Ergot alkaloids**	**-36.9**	**-52.7**	**-21.1**
% women	**Ca channel antagonists**	**Gabapentin**	**-49.3**	**-72.4**	**-26.1**
% women	**Ca channel antagonists**	**Lamotrigine**	**-56.4**	**-93.7**	**-19.0**
% women	**Ca channel antagonists**	**Magnesium**	**-67.6**	**-104.9**	**-30.2**
% women	**Ca channel antagonists**	**Other***	**24.7**	**5.6**	**43.8**
% women	**Ca channel antagonists**	**Oxcarbazepine**	**-59.3**	**-96.6**	**-21.9**

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% women	**Ca channel antagonists**	**Propranolol**	**-52.8**	**-64.9**	**-40.6**
% women	**Ca channel antagonists**	**Tizanidine**	**-53.6**	**-90.9**	**-16.2**
% women	**Ca channel antagonists**	**Topiramate**	**-54.4**	**-66.4**	**-42.4**
% women	**Ca channel antagonists**	**Valproate**	**-57.2**	**-84.6**	**-29.8**
% women	**Ca channel antagonists**	**Vigabatrin**	**-48.5**	**-85.8**	**-11.1**
% women	**Carbamazepine**	**Aspirin**	**68.1**	**17.4**	**118.9**
% women	**Carbamazepine**	**Clonidine**	**61.3**	**24.0**	**98.7**
% women	Carbamazepine	Dihydroergocryptine	-5.6	-47.0	35.8
% women	Carbamazepine	Divalproex	-13.1	-54.5	28.4
% women	Carbamazepine	Ergot alkaloids	6.4	-31.4	44.2
% women	Carbamazepine	Gabapentin	-5.9	-47.3	35.5
% women	Carbamazepine	Lamotrigine	-13.0	-63.7	37.7
% women	Carbamazepine	Magnesium	-24.2	-74.9	26.5
% women	Carbamazepine	Other*	**68.0**	**28.7**	**107.3**
% women	Carbamazepine	Oxcarbazepine	-15.9	-66.6	34.8
% women	Carbamazepine	Propranolol	-9.4	-45.8	27.0
% women	Carbamazepine	Tizanidine	-10.2	-60.9	40.5
% women	Carbamazepine	Topiramate	-11.0	-47.4	25.4
% women	Carbamazepine	Valproate	-13.9	-57.8	30.1
% women	Carbamazepine	Vigabatrin	-5.1	-55.8	45.6
% women	**Clonidine**	**Dihydroergocryptine**	**-66.9**	**-90.1**	**-43.8**
% women	Clonidine	OOther*	6.7	-12.4	25.8
% women	**Clonidine**	**Tizanidine**	**-71.5**	**-108.9**	**-34.2**
% women	**Clonidine**	**Vigabatrin**	**-66.4**	**-103.8**	**-29.1**
% women	dihydroergocryptine	Other*	**73.6**	**47.4**	**99.8**
% women	dihydroergocryptine	Tizanidine	-4.6	-46.0	36.8
% women	dihydroergocryptine	Vigabatrin	0.5	-40.9	41.9
% women	**Divalproex**	**Aspirin**	**81.2**	**39.8**	**122.6**
% women	**Divalproex**	**Clonidine**	**74.4**	**51.2**	**97.5**
% women	Divalproex	Dihydroergocryptine	7.5	-21.8	36.8
% women	Divalproex	Ergot alkaloids	19.5	-4.4	43.4
% women	Divalproex	Gabapentin	7.2	-22.1	36.5
% women	Divalproex	Lamotrigine	0.1	-41.4	41.5
% women	Divalproex	Magnesium	-11.1	-52.6	30.3
% women	**Divalproex**	**Other****	**81.1**	**54.9**	**107.3**
% women	Divalproex	Oxcarbazepine	-2.8	-44.3	38.6
% women	Divalproex	Propranolol	3.7	-18.0	25.3
% women	Divalproex	Tizanidine	2.9	-38.6	44.3
% women	Divalproex	Topiramate	2.1	-19.5	23.6
% women	Divalproex	Valproate	-0.8	-33.5	32.0

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% women	Divalproex	Vigabatrin	8.0	-33.5	49.4
% women	**Ergot alkaloids**	**Aspirin**	**61.7**	**23.9**	**99.5**
% women	**Ergot alkaloids**	**Clonidine**	**54.9**	**39.1**	**70.7**
% women	Ergot alkaloids	Dihydroergocryptine	-12.0	-36.0	11.9
% women	Ergot alkaloids	Gabapentin	-12.3	-36.2	11.6
% women	Ergot alkaloids	Lamotrigine	-19.4	-57.2	18.4
% women	Ergot alkaloids	Magnesium	-30.6	-68.4	7.2
% women	**Ergot alkaloids**	**Other**	**61.6**	**41.6**	**81.6**
% women	Ergot alkaloids	Oxcarbazepine	-22.3	-60.1	15.5
% women	**Ergot alkaloids**	**Propranolol**	**-15.8**	**-29.4**	**-2.3**
% women	Ergot alkaloids	Tizanidine	-16.6	-54.4	21.2
% women	**Ergot alkaloids**	**Topiramate**	**-17.4**	**-30.8**	**-4.0**
% women	Ergot alkaloids	Valproate	-20.3	-48.3	7.8
% women	Ergot alkaloids	Vigabatrin	-11.5	-49.3	26.3
% women	**Gabapentin**	**Aspirin**	**74.0**	**32.6**	**115.4**
% women	**Gabapentin**	**Clonidine**	**67.2**	**44.1**	**90.4**
% women	Gabapentin	Dihydroergocryptine	0.3	-29.0	29.6
% women	Gabapentin	Lamotrigine	-7.1	-48.5	34.3
% women	Gabapentin	Magnesium	-18.3	-59.7	23.1
% women	**Gabapentin**	**Other***	**73.9**	**47.7**	**100.1**
% women	Gabapentin	Oxcarbazepine	-10.0	-51.4	31.4
% women	Gabapentin	Propranolol	-3.5	-25.2	18.2
% women	Gabapentin	Tizanidine	-4.3	-45.7	37.1
% women	Gabapentin	Topiramate	-5.1	-26.7	16.5
% women	Gabapentin	Valproate	-8.0	-40.7	24.8
% women	Gabapentin	Vigabatrin	0.8	-40.6	42.2
% women	**Lamotrigine**	**Aspirin**	**81.1**	**30.4**	**131.9**
% women	**Lamotrigine**	**Clonidine**	**74.3**	**37.0**	**111.7**
% women	Lamotrigine	Dihydroergocryptine	7.4	-34.0	48.8
% women	Lamotrigine	Magnesium	-11.2	-61.9	39.5
% women	**Lamotrigine**	**Other***	**81.0**	**41.7**	**120.3**
% women	Lamotrigine	Oxcarbazepine	-2.9	-53.6	47.8
% women	Lamotrigine	Propranolol	3.6	-32.8	40.0
% women	Lamotrigine	Tizanidine	2.8	-47.9	53.5
% women	Lamotrigine	Topiramate	2.0	-34.4	38.4
% women	Lamotrigine	Valproate	-0.9	-44.8	43.1
% women	Lamotrigine	Vigabatrin	7.9	-42.8	58.6
% women	**Magnesium**	**Aspirin**	**92.3**	**41.6**	**143.1**
% women	**Magnesium**	**Clonidine**	**85.5**	**48.2**	**122.9**
% women	Magnesium	Dihydroergocryptine	18.6	-22.8	60.0

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
% women	**Magnesium**	**Other***	**92.2**	**52.9**	**131.5**
% women	Magnesium	Oxcarbazepine	8.3	-42.4	59.0
% women	Magnesium	Propranolol	14.8	-21.6	51.2
% women	Magnesium	Tizanidine	14.0	-36.7	64.7
% women	Magnesium	Topiramate	13.2	-23.2	49.6
% women	Magnesium	Valproate	10.4	-33.6	54.3
% women	Magnesium	Vigabatrin	19.1	-31.6	69.8
% women	**Other**	**Tizanidine**	**-78.2**	**-117.5**	**-38.9**
% women	**Other**	**Vigabatrin**	**-73.1**	**-112.4**	**-33.8**
% women	**Oxcarbazepine**	**Aspirin**	**84.0**	**33.3**	**134.8**
% women	**Oxcarbazepine**	**Clonidine**	**77.2**	**39.9**	**114.6**
% women	Oxcarbazepine	dihydroergocryptine	10.3	-31.1	51.7
% women	**Oxcarbazepine**	**Other***	**83.9**	**44.6**	**123.2**
% women	Oxcarbazepine	Propranolol	6.5	-29.9	42.9
% women	Oxcarbazepine	Tizanidine	5.7	-45.0	56.4
% women	Oxcarbazepine	Topiramate	4.9	-31.5	41.3
% women	Oxcarbazepine	Valproate	2.1	-41.9	46.0
% women	Oxcarbazepine	Vigabatrin	10.8	-39.9	61.5
% women	**Propranolol**	**Aspirin**	**77.5**	**41.1**	**114.0**
% women	**Propranolol**	**Clonidine**	**70.7**	**58.6**	**82.9**
% women	Propranolol	Dihydroergocryptine	3.8	-17.9	25.5
% women	**Propranolol**	**Other***	**77.4**	**60.2**	**94.7**
% women	Propranolol	Tizanidine	-0.8	-37.2	35.6
% women	Propranolol	Topiramate	-1.6	-10.4	7.2
% women	Propranolol	Valproate	-4.4	-30.6	21.7
% women	Propranolol	Vigabatrin	4.3	-32.1	40.7
% women	Tizanidine	Vigabatrin	5.1	-45.6	55.8
% women	**Topiramate**	**Aspirin**	**79.1**	**42.7**	**115.5**
% women	**Topiramate**	**Clonidine**	**72.3**	**60.3**	**84.3**
% women	Topiramate	Dihydroergocryptine	5.4	-16.2	27.0
% women	**Topiramate**	**Other***	**79.0**	**61.9**	**96.2**
% women	Topiramate	Tizanidine	0.8	-35.6	37.2
% women	Topiramate	Valproate	-2.8	-28.9	23.2
% women	Topiramate	Vigabatrin	5.9	-30.5	42.3
% women	**Valproate**	**Aspirin**	**82.0**	**38.0**	**125.9**
% women	**Valproate**	**Clonidine**	**75.2**	**47.8**	**102.6**
% women	Valproate	Dihydroergocryptine	8.2	-24.5	41.0
% women	**Valproate**	**Other***	**81.9**	**51.9**	**111.9**
% women	Valproate	Tizanidine	3.7	-40.3	47.6
% women	Valproate	Vigabatrin	8.8	-35.2	52.7

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Age	ACE inhibitors	Acetazolamide	0.8	-10.9	12.5
Age	ACE inhibitors	Angiotensin blockers	-5.0	-15.1	5.1
Age	ACE inhibitors	Antidepressant	3.8	-4.7	12.3
Age	ACE inhibitors	Aspirin	0.4	-11.3	12.1
Age	ACE inhibitors	Calcium channel antagonists	2.6	-6.0	11.3
Age	ACE inhibitors	Clonidine	3.3	-5.4	11.9
Age	ACE inhibitors	Dihydroergocryptine	5.7	-4.4	15.8
Age	ACE inhibitors	Divalproex	-2.3	-11.8	7.2
Age	ACE inhibitors	Ergot alkaloids	1.4	-7.3	10.2
Age	ACE inhibitors	Gabapentin	-1.3	-11.4	8.8
Age	ACE inhibitors	Lamotrigine	2.8	-8.9	14.5
Age	ACE inhibitors	Magnesium	-1.0	-12.7	10.7
Age	ACE inhibitors	Other* off label drugs	0.7	-8.5	9.9
Age	ACE inhibitors	Oxcarbazepine	-0.5	-12.2	11.2
Age	ACE inhibitors	Propranolol	2.1	-6.3	10.5
Age	ACE inhibitors	Tizanidine	-0.3	-12.0	11.4
Age	ACE inhibitors	Topiramate	0.9	-7.5	9.2
Age	ACE inhibitors	Valproate	0.0	-10.1	10.1
Age	ACE inhibitors	Vigabatrin	-3.6	-15.3	8.1
Age	Acetazolamide	Antidepressant	3.0	-5.5	11.5
Age	Acetazolamide	Aspirin	-0.4	-12.1	11.3
Age	Acetazolamide	Calcium channel antagonists	1.8	-6.8	10.5
Age	Acetazolamide	Clonidine	2.5	-6.2	11.1
Age	Acetazolamide	Dihydroergocryptine	4.9	-5.2	15.0
Age	Acetazolamide	Divalproex	-3.1	-12.6	6.4
Age	Acetazolamide	Ergot alkaloids	0.6	-8.1	9.4
Age	Acetazolamide	Gabapentin	-2.1	-12.2	8.0
Age	Acetazolamide	Lamotrigine	2.0	-9.7	13.7
Age	Acetazolamide	Magnesium	-1.8	-13.5	9.9
Age	Acetazolamide	Other* off label drugs	-0.1	-9.3	9.1
Age	Acetazolamide	Oxcarbazepine	-1.3	-13.0	10.4
Age	Acetazolamide	Propranolol	1.3	-7.1	9.7
Age	Acetazolamide	Tizanidine	-1.1	-12.8	10.6
Age	Acetazolamide	Topiramate	0.1	-8.3	8.4
Age	Acetazolamide	Valproate	-0.8	-10.9	9.3
Age	Acetazolamide	Vigabatrin	-4.4	-16.1	7.3
Age	Angiotensin blockers	Acetazolamide	5.8	-4.3	15.9
Age	**Angiotensin blockers**	**Antidepressant**	**8.8**	**2.7**	**15.0**
Age	Angiotensin blockers	Aspirin	5.4	-4.7	15.5
Age	**Angiotensin blockers**	**Calcium channel**	**7.6**	**1.3**	**14.0**

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
		antagonists			
Age	**Angiotensin blockers**	**Clonidine**	**8.3**	**1.9**	**14.6**
Age	**Angiotensin blockers**	**Dihydroergocryptine**	**10.7**	**2.5**	**19.0**
Age	Angiotensin blockers	Divalproex	2.7	-4.8	10.2
Age	Angiotensin blockers	Ergot alkaloids	6.4	-0.1	13.0
Age	Angiotensin blockers	Gabapentin	3.7	-4.5	11.9
Age	Angiotensin blockers	Lamotrigine	7.8	-2.3	17.9
Age	Angiotensin blockers	Magnesium	4.0	-6.1	14.1
Age	Angiotensin blockers	Other* off label drugs	5.7	-1.4	12.9
Age	Angiotensin blockers	Oxcarbazepine	4.5	-5.6	14.6
Age	**Angiotensin blockers**	**Propranolol**	**7.1**	**1.1**	**13.2**
Age	Angiotensin blockers	tizanidine	4.7	-5.4	14.8
Age	Angiotensin blockers	Topiramate	5.9	-0.1	11.9
Age	Angiotensin blockers	Valproate	5.0	-3.2	13.2
Age	Angiotensin blockers	vigabatrin	1.4	-8.7	11.5
Age	Antidepressant	aspirin	-3.4	-11.9	5.1
Age	Antidepressant	Calcium channel antagonists	-1.2	-4.5	2.1
Age	Antidepressant	Clonidine	-0.6	-3.9	2.7
Age	Antidepressant	Dihydroergocryptine	1.9	-4.2	8.1
Age	**Antidepressant**	**Divalproex**	**-6.1**	**-11.3**	**-1.0**
Age	Antidepressant	Ergot alkaloids	-2.4	-5.9	1.2
Age	Antidepressant	Gabapentin	-5.1	-11.3	1.0
Age	Antidepressant	Lamotrigine	-1.0	-9.5	7.5
Age	Antidepressant	Magnesium	-4.8	-13.3	3.7
Age	Antidepressant	OOther* off label drugs	-3.1	-7.7	1.5
Age	Antidepressant	Oxcarbazepine	-4.3	-12.8	4.2
Age	Antidepressant	Propranolol	-1.7	-4.2	0.9
Age	Antidepressant	Tizanidine	-4.1	-12.6	4.4
Age	**Antidepressant**	**Topiramate**	**-2.9**	**-5.4**	**-0.5**
Age	Antidepressant	Valproate	-3.8	-10.0	2.3
Age	Antidepressant	Vigabatrin	-7.4	-15.9	1.1
Age	Aspirin	Clonidine	2.9	-5.8	11.5
Age	Aspirin	Dihydroergocryptine	5.3	-4.8	15.4
Age	Aspirin	Other* off label drugs	0.3	-8.9	9.5
Age	Aspirin	Tizanidine	-0.7	-12.4	11.0
Age	Aspirin	Vigabatrin	-4.0	-15.7	7.7
Age	Calcium channel antagonists	Aspirin	-2.2	-10.9	6.4
Age	Calcium channel antagonists	Clonidine	0.6	-3.1	4.3
Age	Calcium channel antagonists	Dihydroergocryptine	3.1	-3.3	9.5
Age	Calcium channel antagonists	Divalproex	-4.9	-10.4	0.5

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Age	Calcium channel antagonists	Ergot alkaloids	-1.2	-5.1	2.7
Age	Calcium channel antagonists	Gabapentin	-3.9	-10.3	2.4
Age	Calcium channel antagonists	Lamotrigine	0.2	-8.5	8.8
Age	Calcium channel antagonists	Magnesium	-3.6	-12.3	5.0
Age	Calcium channel antagonists	Other* off label drugs	-1.9	-6.8	3.0
Age	Calcium channel antagonists	Oxcarbazepine	-3.1	-11.8	5.5
Age	Calcium channel antagonists	Propranolol	-0.5	-3.6	2.5
Age	Calcium channel antagonists	Tizanidine	-2.9	-11.6	5.7
Age	Calcium channel antagonists	Topiramate	-1.8	-4.7	1.2
Age	Calcium channel antagonists	Valproate	-2.6	-9.0	3.7
Age	Calcium channel antagonists	Vigabatrin	-6.2	-14.9	2.4
Age	Clonidine	Dihydroergocryptine	2.5	-3.9	8.9
Age	Clonidine	Other* off label drugs	-2.5	-7.4	2.4
Age	Clonidine	Tizanidine	-3.6	-12.2	5.1
Age	Clonidine	Vigabatrin	-6.9	-15.5	1.8
Age	dihydroergocryptine	Other* off label drugs	-5.0	-12.2	2.1
Age	dihydroergocryptine	Tizanidine	-6.0	-16.1	4.1
Age	dihydroergocryptine	Vigabatrin	-9.3	-19.4	0.8
Age	Divalproex	Aspirin	2.7	-6.8	12.2
Age	**Divalproex**	**Clonidine**	**5.6**	**0.1**	**11.0**
Age	**Divalproex**	**Dihydroergocryptine**	**8.0**	**0.5**	**15.6**
Age	Divalproex	Ergot alkaloids	3.7	-1.8	9.3
Age	Divalproex	Gabapentin	1.0	-6.5	8.5
Age	Divalproex	Lamotrigine	5.1	-4.4	14.6
Age	Divalproex	Magnesium	1.3	-8.2	10.8
Age	Divalproex	Other* off label drugs	3.0	-3.3	9.3
Age	Divalproex	Oxcarbazepine	1.8	-7.7	11.3
Age	Divalproex	Propranolol	4.4	-0.6	9.4
Age	Divalproex	Tizanidine	2.0	-7.5	11.5
Age	Divalproex	Topiramate	3.2	-1.8	8.1
Age	Divalproex	Valproate	2.3	-5.2	9.8
Age	Divalproex	Vigabatrin	-1.3	-10.8	8.2
Age	Ergot alkaloids	Aspirin	-1.0	-9.8	7.7
Age	Ergot alkaloids	Clonidine	1.8	-2.1	5.7
Age	Ergot alkaloids	Dihydroergocryptine	4.3	-2.2	10.8
Age	Ergot alkaloids	Gabapentin	-2.7	-9.3	3.8
Age	Ergot alkaloids	Lamotrigine	1.4	-7.4	10.1
Age	Ergot alkaloids	Magnesium	-2.4	-11.2	6.3
Age	Ergot alkaloids	OOther* off label drugs	-0.7	-5.8	4.3
Age	Ergot alkaloids	Oxcarbazepine	-1.9	-10.7	6.8

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Age	Ergot alkaloids	Propranolol	0.7	-2.6	4.0
Age	Ergot alkaloids	Tizanidine	-1.7	-10.5	7.0
Age	Ergot alkaloids	Topiramate	-0.6	-3.8	2.7
Age	Ergot alkaloids	Valproate	-1.4	-8.0	5.1
Age	Ergot alkaloids	Vigabatrin	-5.0	-13.8	3.7
Age	Gabapentin	Aspirin	1.7	-8.4	11.8
Age	Gabapentin	Clonidine	4.6	-1.8	10.9
Age	Gabapentin	Dihydroergocryptine	7.0	-1.2	15.3
Age	Gabapentin	Lamotrigine	4.1	-6.0	14.2
Age	Gabapentin	Magnesium	0.3	-9.8	10.4
Age	Gabapentin	Other* off label drugs	2.0	-5.1	9.2
Age	Gabapentin	Oxcarbazepine	0.8	-9.3	10.9
Age	Gabapentin	Propranolol	3.4	-2.6	9.5
Age	Gabapentin	Tizanidine	1.0	-9.1	11.1
Age	Gabapentin	Topiramate	2.2	-3.8	8.2
Age	Gabapentin	Valproate	1.3	-6.9	9.5
Age	Gabapentin	Vigabatrin	-2.3	-12.4	7.8
Age	Lamotrigine	Aspirin	-2.4	-14.1	9.3
Age	Lamotrigine	Clonidine	0.5	-8.2	9.1
Age	Lamotrigine	Dihydroergocryptine	2.9	-7.2	13.0
Age	Lamotrigine	Magnesium	-3.8	-15.5	7.9
Age	Lamotrigine	Other* off label drugs	-2.1	-11.3	7.1
Age	Lamotrigine	Oxcarbazepine	-3.3	-15.0	8.4
Age	Lamotrigine	Propranolol	-0.7	-9.1	7.7
Age	Lamotrigine	Tizanidine	-3.1	-14.8	8.6
Age	Lamotrigine	Topiramate	-1.9	-10.3	6.4
Age	Lamotrigine	Valproate	-2.8	-12.9	7.3
Age	Lamotrigine	Vigabatrin	-6.4	-18.1	5.3
Age	Magnesium	Aspirin	1.4	-10.3	13.1
Age	Magnesium	Clonidine	4.3	-4.4	12.9
Age	Magnesium	Dihydroergocryptine	6.7	-3.4	16.8
Age	Magnesium	Other* off label drugs	1.7	-7.5	10.9
Age	Magnesium	Oxcarbazepine	0.5	-11.2	12.2
Age	Magnesium	Propranolol	3.1	-5.3	11.5
Age	Magnesium	Tizanidine	0.7	-11.0	12.4
Age	Magnesium	Topiramate	1.9	-6.5	10.2
Age	Magnesium	Valproate	1.0	-9.1	11.1
Age	Magnesium	Vigabatrin	-2.6	-14.3	9.1
Age	Other off label drugs	Tizanidine	-1.0	-10.2	8.2
Age	Other off label drugs	Vigabatrin	-4.3	-13.5	4.9

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Age	Oxcarbazepine	Aspirin	0.9	-10.8	12.6
Age	Oxcarbazepine	Clonidine	3.8	-4.9	12.4
Age	Oxcarbazepine	Dihydroergocryptine	6.2	-3.9	16.3
Age	Oxcarbazepine	Other* off label drugs	1.2	-8.0	10.4
Age	Oxcarbazepine	Propranolol	2.6	-5.8	11.0
Age	Oxcarbazepine	Tizanidine	0.2	-11.5	11.9
Age	Oxcarbazepine	Topiramate	1.4	-7.0	9.7
Age	Oxcarbazepine	Valproate	0.5	-9.6	10.6
Age	Oxcarbazepine	Vigabatrin	-3.1	-14.8	8.6
Age	Propranolol	Aspirin	-1.7	-10.1	6.7
Age	Propranolol	Clonidine	1.1	-1.9	4.2
Age	Propranolol	Dihydroergocryptine	3.6	-2.4	9.7
Age	Propranolol	Other* off label drugs	-1.4	-5.8	3.0
Age	Propranolol	Tizanidine	-2.4	-10.8	6.0
Age	Propranolol	Topiramate	-1.3	-3.4	0.9
Age	Propranolol	Valproate	-2.1	-8.2	3.9
Age	Propranolol	Vigabatrin	-5.7	-14.1	2.7
Age	Tizanidine	Vigabatrin	-3.3	-15.0	8.4
Age	Topiramate	Aspirin	-0.5	-8.8	7.9
Age	Topiramate	Clonidine	2.4	-0.6	5.3
Age	Topiramate	Dihydroergocryptine	4.9	-1.1	10.9
Age	Topiramate	Other* off label drugs	-0.1	-4.5	4.2
Age	Topiramate	Tizanidine	-1.2	-9.5	7.2
Age	Topiramate	Valproate	-0.9	-6.9	5.1
Age	Topiramate	Vigabatrin	-4.5	-12.8	3.9
Age	Valproate	Aspirin	0.4	-9.7	10.5
Age	Valproate	Clonidine	3.3	-3.1	9.6
Age	Valproate	Dihydroergocryptine	5.7	-2.5	14.0
Age	Valproate	Other* off label drugs	0.7	-6.4	7.9
Age	Valproate	Tizanidine	-0.3	-10.4	9.8
Age	Valproate	Vigabatrin	-3.6	-13.7	6.5
Baseline monthly migraine frequency	ACE inhibitors	Acetazolamide	0.1	-8.6	8.8
Baseline monthly migraine frequency	ACE inhibitors	Ca channel antagonists	-1.0	-7.9	5.9
Baseline monthly migraine frequency	ACE inhibitors	Carbamazepine	2.1	-6.6	10.8
Baseline monthly migraine frequency	ACE inhibitors	Clonidine	1.1	-6.4	8.7
Baseline monthly migraine frequency	ACE inhibitors	Dihydroergocryptine	-0.7	-7.9	6.4

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	ACE inhibitors	Divalproex	-0.7	-9.4	8.0
Baseline monthly migraine frequency	ACE inhibitors	Ergot alkaloids	0.4	-6.2	7.1
Baseline monthly migraine frequency	ACE inhibitors	Gabapentin	0.1	-7.0	7.3
Baseline monthly migraine frequency	ACE inhibitors	Lamotrigine	1.1	-7.6	9.8
Baseline monthly migraine frequency	ACE inhibitors	OOther* off label drugs	0.5	-7.0	8.1
Baseline monthly migraine frequency	ACE inhibitors	Oxcarbazepine	-0.9	-9.6	7.8
Baseline monthly migraine frequency	ACE inhibitors	Propranolol	0.0	-6.3	6.3
Baseline monthly migraine frequency	ACE inhibitors	Topiramate	-2.3	-8.6	3.9
Baseline monthly migraine frequency	ACE inhibitors	Valproate	-0.7	-8.3	6.9
Baseline monthly migraine frequency	ACE inhibitors	Vigabatrin	3.1	-5.6	11.8
Baseline monthly migraine frequency	Acetazolamide	Ca channel antagonists	-1.1	-8.0	5.8
Baseline monthly migraine frequency	Acetazolamide	Carbamazepine	2.0	-6.7	10.7
Baseline monthly migraine frequency	Acetazolamide	Clonidine	1.0	-6.5	8.6
Baseline monthly migraine frequency	Acetazolamide	Dihydroergocryptine	-0.8	-8.0	6.3
Baseline monthly migraine frequency	Acetazolamide	Divalproex	-0.8	-9.5	7.9
Baseline monthly migraine frequency	Acetazolamide	Ergot alkaloids	0.3	-6.3	7.0
Baseline monthly migraine frequency	Acetazolamide	Gabapentin	0.0	-7.1	7.2
Baseline monthly migraine frequency	Acetazolamide	Lamotrigine	1.0	-7.7	9.7
Baseline monthly migraine frequency	Acetazolamide	OOther* off label drugs	0.4	-7.1	8.0
Baseline monthly migraine frequency	Acetazolamide	Oxcarbazepine	-1.0	-9.7	7.7

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	Acetazolamide	Propranolol	-0.1	-6.4	6.2
Baseline monthly migraine frequency	Acetazolamide	Topiramate	-2.4	-8.7	3.8
Baseline monthly migraine frequency	Acetazolamide	Valproate	-0.8	-8.4	6.8
Baseline monthly migraine frequency	Acetazolamide	Vigabatrin	3.0	-5.7	11.7
Baseline monthly migraine frequency	Ca channel antagonists	Carbamazepine	3.1	-3.8	10.0
Baseline monthly migraine frequency	Ca channel antagonists	Clonidine	2.1	-3.2	7.5
Baseline monthly migraine frequency	Ca channel antagonists	Dihydroergocryptine	0.3	-4.4	5.0
Baseline monthly migraine frequency	Ca channel antagonists	Divalproex	0.3	-6.6	7.2
Baseline monthly migraine frequency	Ca channel antagonists	Ergot alkaloids	1.4	-2.5	5.4
Baseline monthly migraine frequency	Ca channel antagonists	Gabapentin	1.1	-3.6	5.9
Baseline monthly migraine frequency	Ca channel antagonists	Lamotrigine	2.1	-4.8	9.0
Baseline monthly migraine frequency	Ca channel antagonists	Other* off label drugs	1.5	-3.8	6.9
Baseline monthly migraine frequency	Ca channel antagonists	Oxcarbazepine	0.1	-6.8	7.0
Baseline monthly migraine frequency	Ca channel antagonists	Propranolol	1.1	-2.3	4.4
Baseline monthly migraine frequency	Ca channel antagonists	Topiramate	-1.3	-4.6	2.0
Baseline monthly migraine frequency	Ca channel antagonists	Valproate	0.3	-5.0	5.7
Baseline monthly migraine frequency	Ca channel antagonists	Vigabatrin	4.1	-2.8	11.0
Baseline monthly migraine frequency	Carbamazepine	Clonidine	-1.0	-8.5	6.6
Baseline monthly migraine frequency	Carbamazepine	Dihydroergocryptine	-2.8	-10.0	4.3
Baseline monthly migraine frequency	Carbamazepine	Divalproex	-2.8	-11.5	5.9

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	Carbamazepine	Ergot alkaloids	-1.7	-8.3	5.0
Baseline monthly migraine frequency	Carbamazepine	Gabapentin	-2.0	-9.1	5.2
Baseline monthly migraine frequency	Carbamazepine	Lamotrigine	-1.0	-9.7	7.7
Baseline monthly migraine frequency	Carbamazepine	OOther* off label drugs	-1.6	-9.1	6.0
Baseline monthly migraine frequency	Carbamazepine	Oxcarbazepine	-3.0	-11.7	5.7
Baseline monthly migraine frequency	Carbamazepine	Propranolol	-2.1	-8.4	4.2
Baseline monthly migraine frequency	Carbamazepine	Topiramate	-4.4	-10.7	1.8
Baseline monthly migraine frequency	Carbamazepine	Valproate	-2.8	-10.4	4.8
Baseline monthly migraine frequency	Carbamazepine	Vigabatrin	1.0	-7.7	9.7
Baseline monthly migraine frequency	Clonidine	Dihydroergocryptine	-1.9	-7.5	3.8
Baseline monthly migraine frequency	Clonidine	OOther* off label drugs	-0.6	-6.8	5.5
Baseline monthly migraine frequency	Clonidine	Vigabatrin	2.0	-5.6	9.5
Baseline monthly migraine frequency	dihydroergocryptine	OOther* off label drugs	1.2	-4.4	6.9
Baseline monthly migraine frequency	dihydroergocryptine	Vigabatrin	3.8	-3.3	11.0
Baseline monthly migraine frequency	Divalproex	Clonidine	1.8	-5.7	9.4
Baseline monthly migraine frequency	Divalproex	Dihydroergocryptine	0.0	-7.2	7.1
Baseline monthly migraine frequency	Divalproex	Ergot alkaloids	1.1	-5.5	7.8
Baseline monthly migraine frequency	Divalproex	Gabapentin	0.8	-6.3	8.0
Baseline monthly migraine frequency	Divalproex	Lamotrigine	1.8	-6.9	10.5
Baseline monthly migraine frequency	Divalproex	Other* off label drugs	1.2	-6.3	8.8

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	Divalproex	Oxcarbazepine	-0.2	-8.9	8.5
Baseline monthly migraine frequency	Divalproex	Propranolol	0.7	-5.6	7.0
Baseline monthly migraine frequency	Divalproex	Topiramate	-1.6	-7.9	4.6
Baseline monthly migraine frequency	Divalproex	Valproate	0.0	-7.6	7.6
Baseline monthly migraine frequency	Divalproex	Vigabatrin	3.8	-4.9	12.5
Baseline monthly migraine frequency	Ergot alkaloids	Clonidine	0.7	-4.3	5.7
Baseline monthly migraine frequency	Ergot alkaloids	Dihydroergocryptine	-1.2	-5.5	3.2
Baseline monthly migraine frequency	Ergot alkaloids	Gabapentin	-0.3	-4.6	4.1
Baseline monthly migraine frequency	Ergot alkaloids	Lamotrigine	0.7	-6.0	7.3
Baseline monthly migraine frequency	Ergot alkaloids	Other* off label drugs	0.1	-4.9	5.1
Baseline monthly migraine frequency	Ergot alkaloids	Oxcarbazepine	-1.3	-8.0	5.3
Baseline monthly migraine frequency	Ergot alkaloids	Propranolol	-0.4	-3.2	2.5
Baseline monthly migraine frequency	Ergot alkaloids	Topiramate	-2.8	-5.5	0.0
Baseline monthly migraine frequency	Ergot alkaloids	Valproate	-1.1	-6.2	3.9
Baseline monthly migraine frequency	Ergot alkaloids	Vigabatrin	2.7	-4.0	9.3
Baseline monthly migraine frequency	Gabapentin	Clonidine	1.0	-4.6	6.6
Baseline monthly migraine frequency	Gabapentin	Dihydroergocryptine	-0.9	-5.9	4.2
Baseline monthly migraine frequency	Gabapentin	Lamotrigine	1.0	-6.2	8.1
Baseline monthly migraine frequency	Gabapentin	Other* off label drugs	0.4	-5.3	6.0
Baseline monthly migraine frequency	Gabapentin	Oxcarbazepine	-1.0	-8.2	6.1

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	Gabapentin	Propranolol	-0.1	-3.9	3.7
Baseline monthly migraine frequency	Gabapentin	Topiramate	-2.5	-6.2	1.3
Baseline monthly migraine frequency	Gabapentin	Valproate	-0.8	-6.5	4.8
Baseline monthly migraine frequency	Gabapentin	Vigabatrin	3.0	-4.2	10.1
Baseline monthly migraine frequency	Lamotrigine	Clonidine	0.0	-7.5	7.6
Baseline monthly migraine frequency	Lamotrigine	Dihydroergocryptine	-1.8	-9.0	5.3
Baseline monthly migraine frequency	Lamotrigine	Other* off label drugs	-0.6	-8.1	7.0
Baseline monthly migraine frequency	Lamotrigine	Oxcarbazepine	-2.0	-10.7	6.7
Baseline monthly migraine frequency	Lamotrigine	Propranolol	-1.1	-7.4	5.2
Baseline monthly migraine frequency	Lamotrigine	Topiramate	-3.4	-9.7	2.8
Baseline monthly migraine frequency	Lamotrigine	Valproate	-1.8	-9.4	5.8
Baseline monthly migraine frequency	Lamotrigine	Vigabatrin	2.0	-6.7	10.7
Baseline monthly migraine frequency	Other off label drugs	Vigabatrin	2.6	-5.0	10.1
Baseline monthly migraine frequency	Oxcarbazepine	Clonidine	2.0	-5.5	9.6
Baseline monthly migraine frequency	Oxcarbazepine	Dihydroergocryptine	0.2	-7.0	7.3
Baseline monthly migraine frequency	Oxcarbazepine	Other* off label drugs	1.4	-6.1	9.0
Baseline monthly migraine frequency	Oxcarbazepine	Propranolol	0.9	-5.4	7.2
Baseline monthly migraine frequency	Oxcarbazepine	Topiramate	-1.4	-7.7	4.8
Baseline monthly migraine frequency	Oxcarbazepine	Valproate	0.2	-7.4	7.8
Baseline monthly migraine frequency	Oxcarbazepine	Vigabatrin	4.0	-4.7	12.7

Appendix Table 11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Variable	Drug group	Drug	Mean difference	Lower 95% CI	Upper 95% CI
Baseline monthly migraine frequency	Propranolol	Clonidine	1.1	-3.5	5.6
Baseline monthly migraine frequency	Propranolol	Dihydroergocryptine	-0.8	-4.6	3.0
Baseline monthly migraine frequency	Propranolol	Other* off label drugs	0.5	-4.1	5.0
Baseline monthly migraine frequency	**Propranolol**	**Topiramate**	**-2.4**	**-4.1**	**-0.6**
Baseline monthly migraine frequency	Propranolol	Valproate	-0.7	-5.3	3.8
Baseline monthly migraine frequency	Propranolol	Vigabatrin	3.1	-3.2	9.4
Baseline monthly migraine frequency	Topiramate	Clonidine	3.5	-1.1	8.0
Baseline monthly migraine frequency	Topiramate	Dihydroergocryptine	1.6	-2.2	5.4
Baseline monthly migraine frequency	Topiramate	Other* off label drugs	2.8	-1.7	7.4
Baseline monthly migraine frequency	Topiramate	Valproate	1.6	-2.9	6.2
Baseline monthly migraine frequency	Topiramate	Vigabatrin	5.4	-0.8	11.7
Baseline monthly migraine frequency	Valproate	Clonidine	1.8	-4.3	8.0
Baseline monthly migraine frequency	Valproate	Dihydroergocryptine	0.0	-5.7	5.6
Baseline monthly migraine frequency	Valproate	Other* off label drugs	1.2	-5.0	7.4
Baseline monthly migraine frequency	Valproate	vigabatrin	3.8	-3.8	11.4

Appendix Table D12. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Trial	Country	Sample [number analyzed] % women	Mean Age	Definition of migraine	Presence of aura, % without aura %	Duration of migraine, months	Baseline severity	Treatment history
Aurora, 2010[1]	PREEMPT NCT00156910	North American	679 [679] 87.5% women	41.7	ICHD-II (2004) section 1, migraine, with the exception of "complicated migraine" (i.e., hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction)	NR % without aura NR	20.4	Migraine episodes: 12.1	% naïve to treatment 38.2 % with prior preventive treatments 61.8
Diener, 2010[2]	PREEMPT NCT00168428	North America & 16 European	705 [705] 85.4% women	41	ICHD-II (2004) section 1, migraine, with the exception of "complicated migraine"	NR % without aura NR	18	Migraine episodes: 12.1	% naïve to treatment 34.9 % with prior preventive treatments 65.1
Saper, 2007[3]	BoNTA-009 Study Group	USA	232 [232] 85.8% women	43.6	Migraine headaches as defined by the International Headache Society criteria	Included % without aura NR	23.8	Migraines per month (historical): 5.7	% naïve to treatment NR % with prior preventive treatments NR
Freitag, 2008[4]		USA	60 [41] 73% women	42.3	Migraine episodes meeting the criteria 1.1 or 1.2 of the ICHD-I	NR % without aura NR	NR	Number of migraine episodes: 14.2	% naïve to treatment NR % with prior preventive treatments NR
Silberstein, 2000[5]	BOTOX Migraine Clinical Research Group	USA	123 [123] 85.4% women	44	Migraine, International Headache Society guideline	Included % without aura NR	NR	Mean migraine frequency: 4.4	% naïve to treatment % naïve to treatment NR % with prior preventive treatments NR
Elkind, 2006[6]	BoNTA-024-026-036 Study	USA	418 [418] 84.7%	44.1	Migraine, International	Included % without	21	Mean Migraine Headache	% naïve to treatment NR

Appendix Table 12. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Trial	Country	Sample [number analyzed] % women	Mean Age	Definition of migraine	Presence of aura, % without aura %	Duration of migraine, months	Baseline severity	Treatment history
	Group		women		Headache Society guideline	aura 50		Frequency: 5.5	% with prior preventive treatments NR
Chankrachang, 2011[7]	NCT00258609	Thailand	128 [Vary] 94.4% women	38.6	International Headache Society (HIS)	% without aura 100	8.2	Migraine attacks per month: 5.1	% naïve to treatment 1.5 % with prior preventive treatments 98.5
Petri, 2009[8]	Dysport Migraine Study Group	Germany	127 [122] 83.6% women	46.2	International Headache Society (HIS)	Included % without aura NR	26.5	Mean attack frequency per month: 4.8	% naïve to treatment NR % with prior preventive treatments NR
Mathew, 2005[9]	BOTOX CDH Study Group	USA	355 [355] 84.5% women	43.5	International Headache Society	Included % without aura NR	Years since onset of CDH: 14.5	Frequency of migraines/probable migraines (month): 11	% naïve to treatment 64.2 % with prior preventive treatments 35.8
Silberstein, 2005[10]		North American	702 [702] 82.9% women	43.4	International Headache Society	Included % without aura NR	Years since onset of CDH: 13.7	Frequency of migraines/probable migraines (month): 10.5	% naïve to treatment 50.4 % with prior preventive treatments 49.6
Anand, 2006[11]		India	32 [32] 75% women	NR	International Headache Society	Included % without aura NR	NR	Mean number of headache days per month: 8.3	% naïve to treatment NR % with prior preventive treatments NR
Cady, 2008[12]		USA	59 [54] 85.2% women	42.1	International Headache Society	Included % without aura 40.6	NR	Mean headache frequency=5.1; headache days=8.4	% naïve to treatment 0 % with prior preventive treatments 100
Vo, 2007[13]	Walter Reed Army Medical Center	USA	32 [32] 84.4% women	42.4	International Headache Society	Included % without aura NR	19.5	Mean migraine frequency (days): 19.4	% naïve to treatment NR % with prior

Appendix Table 12. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Trial	Country	Sample [number analyzed] % women	Mean Age	Definition of migraine	Presence of aura, % without aura %	Duration of migraine, months	Baseline severity	Treatment history
	Neurology trial								preventive treatments NR
Aurora, 2007[14]	BOTOX North American Episodic Migraine Study Group	North American	369 [369] 89.2% women	45	International Headache Society	Included % without aura NR	22.7	Migraine headache episodes per month: 6.5	% naïve to treatment 61.8 % with prior preventive treatments 38.2
Barrientos, 2003[15]		Chile (Unclear)	30 [30] 80% women	41.1	International Headache Society	Included % without aura NR	15.1	Frequency of migraine attacks (month): 5.1	% naïve to treatment NR % with prior preventive treatments NR
Relja, 2007[16]	European BoNTA Headache Study Group	European countries (Belgium, Croatia, Denmark, Finland, France, Germany, Norway, Switzerland, UK)	515 [515] 87.9% women	43.2	International Headache Society (HIS)	Included % without aura NR	Mean time since first migraine onset (years): 23.1	Mean number of days of acute medication use: 6.2	% naïve to treatment 42.4 % with prior preventive treatments 57.6

NR - not reported

Appendix Table D13. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Finance	Ethical approval	Consent	Conflict of interest	Conflict of interest disclosure
Aurora, 2010[1]	Industry	Yes	Yes	Yes	SKA has received grants and research support from Advanced Bionics, Alexza, Allergan, Capnia, GlaxoSmithKline, MAP pharmaceuticals, Merck, Ortho-McNeil, Neuralieve, NuPathe and Takeda. She is a consultant for Ortho-McNeil, Merck, GlaxoSmithKline, Allergan, Neuralieve, NuPathe and MAP Pharmaceuticals. She has also received honoraria from Merck, GlaxoSmithKline, Kowa, NuPathe and Ortho-McNeil. DWD has received honoraria from Allergan, Merck, Neuralieve, Coherex, Kowa, Minster, NeurAxon, H Lundbeck, Endo, Pfizer, Nupathe and MAP Pharmaceuticals, in addition to being a consultant to and on the advisory board of these pharmaceutical companies. He has also received funding from Advanced Neurostimulation Systems, St. Jude Medical Center and Medtronic. CCT, RED and MFB are employees of Allergan, and own stock in the company. SDS and RBL have received honoraria and research funding from Allergan, in addition to being consultants to and on the advisory board of Allergan. HCD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Bohringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grunenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brummer, Sanofi-Aventis and Weber & Weber. He has also received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer. Headache research at the Department of Neurology in Essen, where HCD is Professor, is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union.
Diener, 2010[2]	Industry	Yes	Yes	Yes	HCD has received honoraria for participation in clinical trials, contribution to advisory boards and/or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Bohringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grunenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brummer, Sanofi-Aventis and Weber & Weber. He has also received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag and Pfizer. Headache research at the Department of Neurology in Essen, where HCD is professor, is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union. DWD has received honoraria from Allergan, Merck, Neuralieve, Coherex, Kowa, Minster, NeurAxon, H Lundbeck, Endo, Pfizer, Nupathe and MAP Pharmaceuticals, in addition to being a consultant to and on the advisory board of these pharmaceutical companies. He has also received funding from Advanced Neurostimulation Systems, St. Jude Medical Center and Medtronic. SKA received grants and research support from Advanced Bionics, Alexza, Allergan, Capnia, GlaxoSmithKline, MAP Pharmaceuticals, Merck, Ortho-McNeil, Neuralieve, NuPathe and Takeda. She is a consultant for Ortho-McNeil, Merck, GlaxoSmithKline, Allergan,

Appendix Table 13. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Finance	Ethical approval	Consent	Conflict of interest	Conflict of interest disclosure
					Neuralieve, NuPathe and MAP Pharmaceuticals. She has also received honoraria from Merck, GlaxoSmithKline, Kowa, NuPathe and Ortho-McNeil. CCT, RED and MFB are employees of Allergan, and own stock in the company. SDS and RBL have received honoraria and research funding from Allergan, in addition to being consultants to and on the advisory board of Allergan.
Saper, 2007[3]	Industry	No	Yes	Yes	Two authors are employed by Allergan, Inc.
Freitag, 2008[4]	Industry	Yes	Yes	Yes	Dr. Freitag has received grant support and consulting fees from Allergan.
Silberstein, 2000[5]	Industry	Yes	Yes	Yes	One author is employed by Allergan Inc, study funder.
Elkind, 2006[6]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan Inc, study funder.
Chankrachang, 2011[7]	Industry	Yes	Yes	No	Not applicable
Petri, 2009[8]	Industry	Yes	Yes	Yes	One of the authors (Ceballos-Baumann) has received honoraria for speeches from Ipsen Pharma and from other companies that manufacture botulinum toxin,
Mathew, 2005[9]	Industry	Yes	Yes	Yes	R.Dimitrova, J.Gibson, and C.Turkel are employed by Allergan, Inc., and own stock in the company
Silberstein, 2005[10]	Industry	Yes	Yes	Yes	Dr. Silberstein is on the advisory panel and speakers' bureau and receives research support from Allergan, Inc; Dr Stark has served as a principal investigator and subinvestigator for Allergan, Inc, for the past 4 years. Dr Lucas is a consultant for Allergan, Inc. Dr Christie has received a research grant, consultancy fees, and honoraria from Allergan, Inc. Dr Turkel and Mr DeGryse are employed by and own stock in Allergan, Inc.
Anand, 2006[11]	Not reported	Yes	Yes	Not reported	Not applicable
Cady, 2008[12]	Industry	Yes	Yes	Not reported	Not applicable
Vo, 2007[13]	Grant	Yes	Yes	Not reported	Alexander Vo is an employee of Uniformed Services University of the Health Sciences (sponsor of the study)
Aurora, 2007[14]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan, Inc, and own stock in the company.
Barrientos, 2003[15]	Industry	Yes	Yes	Not reported	Not applicable
Relja, 2007[16]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan, Inc. and own stock in the company.

Appendix Table D14. Risk of bias in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Masking	Intention to treat planned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias	Other biases
Aurora, 2010[1]	Double blind	Yes	Adequate	No	Unclear	Moderate	Mean headache episodes during baseline & Mean migraine episodes during baseline are statistically different between group
Diener, 2010[2]	Double blind	Yes	Adequate	Yes	Unclear	Low	
Saper, 2007[3]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Freitag, 2008[4]	Double blind	Yes	Unclear	Unclear (no tests conducted)	Unclear	Low	Poor reporting quality
Silberstein, 2000[5]	Double blind	Yes	Unclear	No	Unclear	Moderate	Mean age differs by group: patients in vehicle group had higher mean age; Baseline frequencies of migraines of any severity were significantly lower in the 75-U BTX-A treatment group (4.40) than in the 25-U BTX-A (5.48) or vehicle (5.20) groups (P<.046). There was a statistically significant difference among groups in time since onset of migraines (P,.001), with a greater mean time since onset in the vehicle (27.4 years) and 25-U BTX-A (23.4 years) groups than in the 75-U BTX-A group (16.9 years).
Elkind, 2006[6]	Double blind	Yes	Unclear	Yes (See note)	Unclear	Low	
Chankrachang, 2011[7]	Double blind	Yes	Unclear	Yes	Unclear	Low	ITT planned only for efficacy measures
Petri, 2009[8]	Double blind	Yes	Unclear	No	Yes	High	Mean age differs by groups
Mathew, 2005[9]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Silberstein, 2005[10]	Double blind	Yes	Unclear	Yes	Unclear	Low	does not provide loss at follow-up
Anand, 2006[11]	Double blind	No	Unclear	Unclear (Table Dis not provided, but	Unclear	Moderate	Concern regarding baseline severity: in text, authors

Appendix Table 14. Risk of bias in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Masking	Intention to treat planned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias	Other biases
				authors mentioned "Demographic characteristics of patients in both the groups were comparable".			report mean number of headache days at baseline (4 moderate to severe headache in trt group vs. 12.6 in placebo group)
Cady, 2008[12]	Double blind	No	Unclear	Yes	Unclear	Low	
Vo, 2007[13]	Double blind	No	Unclear	Yes	Unclear	Low	primary reason for attrition is attributable due the fluidality of personnel in a major military medical setting during a time of conflict
Aurora, 2007[14]	Double blind	Yes	Unclear	No	Unclear	Moderate	
Barrientos, 2003[15]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Relja, 2007[16]	Double blind	Yes	Unclear	Yes	Unclear	Low	

Appendix Table D15. Strength of evidence of decrease in migraine frequency of at least 50% with botox

Reference	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Silberstein, 2000[5]	Moderate	Yes			
Freitag, 2008[4]	Low	Yes			
Mathew, 2005[9]	Low	Yes			
Overall	Moderate	Yes	Yes	No	Low

Appendix Table D16. Decrease in migraine frequency of at least 50% with botox, pooled results from randomized controlled clinical trials, random effects models with inverse variance weights

Dose of drug Duration of active treatment in weeks	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
25U 12 weeks	Silberstein, 2000[5] Moderate	19/42	5/21	1.9 (0.8 to 4.4)	6.88	0.21 (-0.02 to 0.45)	13.85
100U 16 weeks	Freitag, 2008[4] Low	6/20	3/21	2.1 (0.6 to 7.3)	3.1	0.16 (-0.09 to 0.41)	12.33
105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	94/173	69/182	1.4 (1.1 to 1.8)	90.02	0.16 (0.06 to 0.27)	73.82
28 weeks	Pooled	119/235	77/224	1.5 (1.2 to 1.8)	100	0.17 (0.08 to 0.26)	100

Appendix Table D17. Migraine headache frequency (change from baseline) with botox, pooled results from randomized controlled clinical trials, random effects models

Reference	Dose, weeks of treatment	Sample in active [control]	Mean [standard deviation] with botox	Mean [standard deviation] with placebo	Cohen mean difference	Weight	Mean difference (95% CI)	Weight	Mean ratio (95% CI)	Weight
Elkind, 2006[6]	7.5U 4 weeks	105 [106]	-1.5 [2.6]	-1.3 [2.4]	-0.1 (-0.3 to 0.2)	8.02	-0.2 (-0.9 to 0.5)	7.6	1.1 (0.7 to 1.8)	7.91
	7.5U 8 weeks	105 [106]	-1.6 [2.2]	-1.4 [2.3]	-0.1 (-0.3 to 0.2)	8.02	-0.2 (-0.8 to 0.4)	9.55	1.1 (0.7 to 1.7)	11.31
	7.5U 12 weeks	105 [106]	-1.4 [2.6]	-1.2 [2.6]	-0.1 (-0.3 to 0.2)	8.02	-0.1 (-0.8 to 0.6)	7.09	1.1 (0.6 to 1.9)	6.08
	7.5U 16 weeks	105 [106]	-1.5 [2.6]	-1.5 [2.4]	0.0 (-0.3 to 0.3)	8.02	0.0 (-0.7 to 0.7)	7.81	1.0 (0.6 to 1.6)	9.11
	25U 4 weeks	101 [106]	-1.4 [2.2]	-1.3 [2.4]	0.0 (-0.3 to 0.3)	7.87	0.0 (-0.7 to 0.6)	8.62	1.0 (0.6 to 1.6)	8.01
	25U 8 weeks	101 [106]	-1.4 [2.7]	-1.4 [2.3]	0.0 (-0.2 to 0.3)	7.87	0.1 (-0.6 to 0.7)	7.56	1.0 (0.6 to 1.6)	7.72
	25U 12 weeks	101 [106]	-1.3 [2.6]	-1.2 [2.6]	0.0 (-0.3 to 0.2)	7.86	-0.1 (-0.8 to 0.6)	7.17	1.1 (0.6 to 1.9)	5.98
	25U 16 weeks	101 [106]	-1.0 [2.7]	-1.5 [2.4]	0.2 (-0.1 to 0.5)	7.83	0.5 (-0.2 to 1.2)	7.2	0.7 (0.4 to 1.2)	5.1
	50U 4 weeks	106.0 [106]	-1.1 [2.2]	-1.3 [2.4]	0.1 (-0.2 to 0.4)	8.05	0.2 (-0.4 to 0.8)	9.03	0.8 (0.5 to 1.4)	6.94
	50U 8 weeks	106.0 [106]	-1.2 [2.4]	-1.4 [2.3]	0.1 (-0.1 to 0.4)	8.05	0.3 (-0.3 to 0.9)	8.67	0.8 (0.5 to 1.3)	7.15
	50U 12 weeks	106.0 [106]	-1.4 [2.3]	-1.2 [2.6]	-0.1 (-0.3 to 0.2)	8.06	-0.1 (-0.8 to 0.5)	8	1.1 (0.7 to 1.9)	6.78
	50U 16 weeks	106.0 [106]	-1.6 [2.5]	-1.5 [2.4]	0.0 (-0.3 to 0.2)	8.06	-0.1 (-0.7 to 0.6)	8.12	1.0 (0.7 to 1.6)	9.79
Chankrachang, 2011[7]	240U 12 (one time injection) weeks	43.0 [21]	1.8 [3.2]	2.2 [2.6]	-0.1 (-0.7 to 0.4)	2.14	-0.4 (-1.9 to 1.1)	1.6	0.8 (0.4 to 1.7)	3.41
	120U 12 (one time injection) weeks	43.0 [21]	2.0 [2.4]	2.2 [2.6]	-0.1 (-0.6 to 0.4)	2.14	-0.3 (-1.6 to 1.0)	1.99	0.9 (0.5 to 1.6)	4.71
Pooled					0.0 (-0.1 to 0.1)	100	0.0 (-0.2 to 0.2)	100	-0.02 (-0.15 to 0.12)	100

Appendix Table D18. Severity, disability, and quality of life with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials)

Definition	Reference	Dose, Weeks of treatment	Sample Active [control]	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen Mean difference (95% CI)	P value	Mean difference (95% CI)
Migraine Disability Assessment Scores (MIDAS)	Freitag, 2008[4]	100U 16weeks	20.0 [21]	51.0 [0.0]	63.0 [0.0]		0.445	
Headache Pain Specific QoL (no information on scale)	Freitag, 2008[4]	100U 16weeks	20.0 [21]	178.0 [0.0]	191.0 [0.0]		0.078	
Change in Migraine Disability Assessment (MIDAS) from baseline	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-21.6 [38.7]**	**4.8 [18.9]**	**-0.8 (-1.3 to -0.2)**		**-26.4 (-41.1 to -11.7)**
Change in Migraine Impact Questionnaire (MIQ): Global assessment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**2.0 [1.4]**	**0.9 [1.5]**	**0.8 (0.2 to 1.3)**		**1.1 (0.3 to 1.9)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of non-Rx treatment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.1 [1.2]**	**-0.3 [1.5]**	**1.1 (0.5 to 1.7)**		**1.5 (0.7 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of Rx treatment	Cady, 2008[12]	139 U 12 (one time injection)weeks	40.0 [19]	0.5 [1.6]	0.4 [1.4]	0.0 (-0.5 to 0.6)		0.1 (-0.7 to 0.9)
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of current Treatment on frequency of migraine symptoms	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.4 [1.7]**	**0.0 [1.3]**	**0.9 (0.3 to 1.4)**		**1.4 (0.6 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of current Treatment on severity of migraine symptoms	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.5 [1.8]**	**0.1 [1.4]**	**0.9 (0.3 to 1.4)**		**1.4 (0.6 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Feelings with current preventive migraine treatment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.7 [1.9]**	**0.4 [1.9]**	**0.7 (0.1 to 1.3)**		**1.3 (0.3 to 2.3)**

Appendix Table 18. Severity, disability, and quality of life with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of treatment	Sample Active [control]	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen Mean difference (95% CI)	P value	Mean difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ): Side effects of current preventive migraine treatment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.7 [1.8]**	**0.5 [1.6]**	**0.7 (0.1 to 1.3)**		**1.2 (0.3 to 2.1)**
Change in Migraine Impact Questionnaire (MIQ): Number of doses required for migraine preventive treatment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.3 [2.0]**	**-0.2 [1.7]**	**0.8 (0.2 to 1.3)**		**1.4 (0.5 to 2.4)**
Change in Migraine Impact Questionnaire (MIQ): Overall effectiveness of current migraine preventive treatment	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.4 [2.1]**	**0.1 [0.9]**	**0.7 (0.2 to 1.3)**		**1.3 (0.5 to 2.1)**
Change in Migraine Impact Questionnaire (MIQ): Ability to self-manage migraine symptoms	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.0 [1.3]**	**-0.1 [1.3]**	**0.8 (0.3 to 1.4)**		**1.1 (0.4 to 1.8)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.5 [1.2]	-0.2 [1.1]	-0.3 (-0.8 to 0.3)		-0.3 (-1.0 to 0.3)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.8 [1.2]	-0.3 [1.1]	-0.4 (-1.0 to 0.1)		-0.5 (-1.1 to 0.1)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.1 [1.2]**	**-0.4 [0.9]**	**-0.7 (-1.2 to -0.1)**		**-0.7 (-1.3 to -0.2)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	Cady, 2008[12]	139 U 12 (one time injection)weeks	40.0 [19]	-0.5 [1.1]	-0.1 [1.1]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	**Cady, 208[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.7 [1.1]**	**0.1 [0.9]**	**-0.8 (-1.3 to -0.2)**		**-0.8 (-1.3 to -0.2)**

Appendix Table 18. Severity, disability, and quality of life with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of treatment	Sample Active [control]	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen Mean difference (95% CI)	P value	Mean difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.6 [1.1]**	**0.2 [0.8]**	**-0.8 (-1.3 to -0.2)**		**-0.8 (-1.3 to -0.3)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.3]	-0.4 [0.8]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.8 [1.1]**	**-0.1 [1.2]**	**-0.6 (-1.2 to -0.1)**		**-0.7 (-1.3 to -0.1)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.8 [1.0]**	**-0.2 [0.8]**	**-0.6 (-1.2 to -0.1)**		**-0.6 (-1.1 to -0.1)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.1]	-0.4 [0.9]	-0.4 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.9 [1.1]**	**-0.1 [0.9]**	**-0.7 (-1.3 to -0.1)**		**-0.8 (-1.3 to -0.2)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.1 [1.0]**	**-0.3 [0.8]**	**-0.8 (-1.4 to -0.2)**		**-0.8 (-1.3 to -0.3)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.5 [1.1]	0.1 [0.9]	-0.6 (-1.1 to 0.0)		-0.6 (-1.1 to -0.1)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.6 [1.0]**	**0.3 [1.0]**	**-0.9 (-1.5 to -0.3)**		**-0.9 (-1.5 to -0.4)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.9 [1.0]**	**0.2 [1.2]**	**-1.0 (-1.6 to -0.4)**		**-1.1 (-1.7 to -0.5)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.6 [1.2]	-0.2 [1.0]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	Cady, 2008[12]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.3]	0.0 [1.1]	-0.6 (-1.1 to 0.0)		-0.7 (-1.3 to 0.0)

Appendix Table 18. Severity, disability, and quality of life with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of treatment	Sample Active [control]	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen Mean difference (95% CI)	P value	Mean difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	**Cady, 2008[12]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.0 [1.1]**	**-0.2 [1.1]**	**-0.7 (-1.3 to -0.1)**		**-0.8 (-1.3 to -0.2)**
Beck's Depression Inventory (BDI)	Petri, 2009[8]	210U 12 (one time injection) weeks	32.0 [32]				No differences	
Beck's Depression Inventory (BDI)	Petri, 2009[8]	80U 12 (one time injection) weeks	32.0 [32]				No differences	
Change from baseline in total Headache Impact Test-6 (HIT-6) score	**Aurora, 2010[1]**	**155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks**	**341.0 [338]**	**-4.7 [0.0]**	**-2.4 [0.0]**		**<.001**	
Change from baseline in total Headache Impact Test-6 (HIT-6) score	**Diener, 2010[2]**	**155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks**	**347.0 [358]**	**-4.9 [-2.4]**			**<.001**	
Severity of headache (VAS 10-point, 10 indicate no pain)	**Anand, 2006[11]**	**50U 12 (one treatment) weeks**	**16.0 [16]**	**7.3 [3.0]**	**2.6 [1.0]**	**2.1 (1.2 to 3.0)**		**4.7 (3.1 to 6.2)**
Severity of headache (VAS 10-point, 10 indicate no pain)	**Anand, 2006[11]**	**50U 12 (one treatment) weeks**	**16.0 [16]**	**7.6 [3.2]**	**2.7 [1.1]**	**2.1 (1.2 to 2.9)**		**4.9 (3.2 to 6.5)**
Severity of pain	Vo, 2007[13]	Differs by weight: 1) < 65 kg: 135 U; 2) ≥ 65 kg: 205 U GLM Repeated measure analysis of variance during 12 weeks	15.0 [17]				Not significant	
Mean severity of migraines (change from	**Silberstein, 2000[5]**	**25U**	**42.0 [21]**				**Significantly greater**	

Appendix Table 18. Severity, disability, and quality of life with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of treatment	Sample Active [control]	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen Mean difference (95% CI)	P value	Mean difference (95% CI)
baseline)							**reduction in the 25U group than in the vehicle group at week 4 & week 8 (≤0.029).**	
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	240U 12 (one time injection) weeks	43.0 [21]	-14.6 [74.3]	-10.5 [22.8]	-0.1 (-0.6 to 0.5)		-4.1 (-28.3 to 20.2)
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	240U 12 (one time injection) weeks	43.0 [21]	-11.3 [85.5]	-5.2 [39.3]	-0.1 (-0.6 to 0.4)		-6.1 (-36.7 to 24.5)
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	240U 12 (one time injection) weeks	43.0 [21]	-22.3 [83.4]	-9.7 [53.0]	-0.2 (-0.7 to 0.4)		-12.5 (-46.2 to 21.2)
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	120U 12 (one time injection) weeks	43.0 [21]	-14.9 [35.9]	-10.5 [22.8]	-0.1 (-0.7 to 0.4)		-4.4 (-18.9 to 10.1)
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	120U 12 (one time injection) weeks	43.0 [21]	-10.7 [49.9]	-5.2 [39.3]	-0.1 (-0.6 to 0.4)		-5.5 (-27.9 to 17.0)
Change in the mean total intensity score (no details) from baseline	Chankrachang, 2011[7]	120U 12 (one time injection) weeks	43.0 [21]	-16.1 [32.5]	-9.7 [53.0]	-0.2 (-0.7 to 0.4)		-6.4 (-31.0 to 18.2)

Bold – significant differences at 95% CL
CI – confidence interval

Appendix Table D19. Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	Country	Design	Total sample [Number analyzed] % females	Age of subjects (mean or median)	Definition of migraine	Presence of aura	Duration of migraine	Headache frequency at baseline/ month	Concomitant treatments
Storey, 2001[17]	Not reported	Randomized controlled clinical trial	40 [Not reported] 97.5% female	Mean 38.2 years	International Headache Society (IHS) criteria	Not reported	Not reported	4.7	Not reported
Edwards, 2003[18]	Previously reported	Randomized controlled clinical trial	70 [70] 97.1% female	Mean 41.1 years	International Headache Society criteria	Not reported	Not reported	4.5	Not reported
Silvestrini, 2003[19]	Italy	Randomized controlled clinical trial	28 [28] 64.3% female	Mean 43.5 years	International Headache Society criteria	All patients had a history of migraine without aura attacks as inclusion criterion	3 years	20	Not reported
Silberstein, 2003[20]	Not reported	Randomized controlled clinical trial	469 [Not reported] % females not reported	Not reported	International Headache Society criteria	Not reported	At least 6 months	2 to 12	Not reported
Brandes, 2004[21]	North America	Randomized controlled clinical trial	483 [468] 86.8% female	Mean 38.9 years	International Headache Society (IHS) criteria	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2004[22]	USA	Randomized controlled clinical tria	487 [469] 89.1% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2004[23]	Italy	Randomized controlled clinical trial	115 [72] 54.2% female	Mean 39.2 years	International Headache Society (1988) criteria	Patients with migraine without aura, n (%): Topiramate: 27 (77), Placebo: 31 (84)	Not reported	5.5	Subjects on continuing medication for other pathologies were included and did not modify the dosages during the study

Appendix Table 19 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total sample [Number analyzed] % females	Age of subjects (mean or median)	Definition of migraine	Presence of aura	Duration of migraine	Headache frequency at baseline/ month	Concomitant treatments
Bussone, 2005[24]	Not reported	Randomized controlled clinical trial (Pooled analysis)	758 [756] 84.3% female	Mean 39.8 years	International Headache Society criteria	Not reported	Not reported	5.4	Not reported
Diamond, 2005[25]	Not reported	Randomized controlled clinical trial	756 [756] 84.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	3 to 12	Not reported
Silberstein, 2006[26]	USA	Randomized controlled clinical trial	469 [469] 88.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2006[27]	Italy	Randomized controlled clinical trial	50 [35] 68.6% female	Mean 45.9 years	International Classification of Headache Disorders 2nd Edition	Not reported	4.97 years	Not reported	Not reported
Silberstein, 2006[28]	USA	Randomized controlled clinical trial	213 [Variable] 85.8% female	Mean 40.5 years	International Headache Society criteria	75 subjects had migraine with aura	Not reported	4.9	Not reported
Brandes, 2006[29]	USA	Randomized controlled clinical trial	483 [468] 86.8% female	Mean 38.9 years	International Headache Society criteria for migraine with or without aura	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2007[30]	USA	Randomized controlled clinical trial	328 [Variable] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration: 9.2 years; Age at onset: 19.7 years	Not reported	Not reported
Lofland, 2007[31]	North America	Randomized controlled clinical trial	325 [325] 89.0% female	Mean 40 years	International Headache Society criteria	Not reported	Not reported	3 to 12	Not reported
Limmroth, 2007[32]	Not reported	Randomized controlled clinical trial	756 [756] 84.0% female	Mean 40 years	International Headache Society criteria	Not reported	Not reported	7.3	Not reported
Diener, 2007[33]	Not reported	Randomized controlled clinical trial	59 [59] 74.5% female	Mean 46 years	Second edition of The International	Not reported	At least 1 year	Not reported	Not reported

Appendix Table 19 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total sample [Number analyzed] % females	Age of subjects (mean or median)	Definition of migraine	Presence of aura	Duration of migraine	Headache frequency at baseline/ month	Concomitant treatments
					Classification of Headache Disorders criteria				
Lainez, 2007[34]	Not reported	Randomized controlled clinical trial	774 [758] 84.4% female	Mean 39.9 years	Interantional Headache Society criteria	Not reported	Not reported	Not reported	Not reported
Freitag, 2007[35]	USA	Randomized controlled clinical trial (Pooled analysis)	937 [937] 87.7% female	Mean 39.7 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Dahlof, 2007[36]	Not reported	Randomized controlled clinical trial	756 [756] 84.3% female	Mean 39.8 years	Not reported	Not reported	Not reported	3 to 12	Not reported
Diener, 2007[37]	21 countries in Europe	Randomized controlled clinical trial	818 [Not reported] 89.0% female	Mean 40·1 years	International Headache Society criteria	Not reported	Not reported	8.7	Not reported
Dodick, 2007[38]	USA	Randomized controlled clinical trial	328 [306] 85.3% female	Mean 38.2 years	International Classification of Headache Disorders, 2nd edition (ICHD-II). However, for the inclusion criterion chronic migraine was defined by Silberstein–Lipton criteria	Not reported	Age at onset: 19.7 years	Not reported	Not reported
Adelman, 2008[39]	USA, Australia, Canada, Denmark, Finland, France, Germany,	Randomized controlled clinical trial	1580 [1580] 85.0% female	Mean 40.1 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported

Appendix Table 19 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total sample [Number analyzed] % females	Age of subjects (mean or median)	Definition of migraine	Presence of aura	Duration of migraine	Headache frequency at baseline/ month	Concomitant treatments
	Italy, Korea, the Netherlands, South Africa, Spain, Sweden, Taiwan, and the United Kingdom								
Silberstein, 2009[40]	USA	Randomized controlled clinical trial	328 [321] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration: 9.2 years; Age at onset: 19.7 years	Not reported	Not reported
Lipton, 2011[41]	Not reported	Randomized controlled clinical trial	385 [Variable] 10.9% female	Mean 40.3 years	International Headache Society criteria 1.1,1.2	Not reported	Age at migraine onset:: 20.3 years	Not reported	Not reported

Appendix Table D20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
Storey, 2001[17]	Industry	Yes	Yes	Not reported	Not applicable
Edwards, 2003[18]	Industry	Yes	Yes	Yes	Ms. Potter is on the Speakers' Bureau for biogen, GlaxoSmithKline and Ortho-McNeil Pharmaceutical, Inc, and has received funding from Biogen, Ortho-McNeil Pharmaceutical, Inc, Pfizer Inc, Wyeth Pharmaceuticals for previous research
Silvestrini, 2003[19]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2003[20]	Not reported	Not reported	Not reported	Not reported	Not applicable
Brandes, 2004[21]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, Allergan, UCB Pharma, Johnson & Johnson, AstraZeneca, Pfizer, Bristol Myers-Squibb, Winston Laboratories, Forest Laboratories, Sanofi-Synthelabo, and Elan Pharmaceuticals; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Merck, Allergan, Pfizer, Pharmacia, Ortho-McNeil, and UCB Pharma; has served as a consultant to Merck, GlaxoSmithKline, Pfizer, AstraZeneca, Allergan, and Ortho-McNeil; and has received educational funding from GlaxoSmithKline. Dr Saper has received research grants from GlaxoSmithKline, AstraZeneca, Merck, Abbott, Allergan, Elan, Pfizer, Ortho-McNeil, and Novartis; has served on advisory boards or as a consultant for AstraZeneca, GlaxoSmithKline, Allergan, Ortho-McNeil, and Medtronic; and has served on the speakers bureau for GlaxoSmithKline, Merck, AstraZeneca, Ortho-McNeil, Pfizer, and Xcel. Dr Diamond has served as a speaker, consultant, or both or has conducted research for AstraZeneca, Bristol-Myers Squibb, Ortho- McNeil, Elan, GlaxoSmithKline, Merck, and Pfizer. Dr Couch has participated in research for, been an advisory board member of, and served as a speaker for Ortho-McNeil.
Silberstein, 2004[22]	Industry	Yes	Yes	Yes	Dr. Silberstein is on the advisory panel of, speakers bureau of, or serves as a consultant for Abbott Laboratories, Allergan, Inc, AstraZeneca, Elan Pharmaceutical Research Corp, Eli Lilly, Ortho-

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					McNeil Pharmaceutical, Merck & Co, and GlaxoSmithKline; receives research support from Allergan, Inc, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Merck & Co, Ortho-McNeil Pharmaceutical, Pfizer, Inc, UCB Pharma, and Vernalis; and has received educational grants from Abbott Laboratories, Allergan, Inc, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck & Co, Ortho-McNeil Pharmaceutical, and Parke-Davis. Drs Neto and Jacobs and Ms Schmitt hold shares in Johnson & Johnson Pharmaceutical Research and Development, LLC, a subsidiary of Johnson & Johnson Corporation.
Mei, 2004[23]	Not reported	Yes	Yes	Not reported	Not applicable
Bussone, 2005[24]	Not reported	Yes	Yes	Not reported	Not applicable
Diamond, 2005[25]	Industry	Yes	Yes	Not reported, however, George Papadopoulos is from Jonhson & Johnson Pharmaceutical Services, LLC, Raritan, NJ; Dr. Neto is from Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ; and Dr. Wu is from Ortho-McNeil Neurologies, Inc., Raritan, NJ	
Silberstein, 2006[26]	Industry	Yes	Yes	Yes	George Papadopoulos is from Johnson and Johnson Pharmaceutical Services, LLC, Raritan, NJ, USA and Steven Greenberg from Ortho-McNeil Neurologies, Titusville, NJ, USA. Personnel of Pharmaceutical Research and Development , Ortho-McNeil Neurologics, Inc, Titusville, New Jersey, and Phase Five Communications, New York, New York, contributed to the preparation of the manuscript
Mei, 2006[27]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[28]	Industry	Yes	Yes	Not reported	Not applicable

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
Brandes, 2006[29]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck & Co, Inc, GlaxoSmithKline, UCB Pharma, Allergan Inc, Johnson & Johnson, Astra-Zeneca Pharmaceuticals LP, Pfizer Inc, Bristol-Meyers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Inc, Novartis, Endo Pharmaceuticals, Pozen, Vernalis, Ortho-McNeil, and Advanced Bionics; has served on the speaker's bureau for GlaxoSmith-Kline, AstraZeneca Pharmaceuticals LP, Pfizer Inc, Merck & Co, Inc, Ortho-McNeil, Allergan Inc, MedPointe Pharmaceuticals, Endo Pharmaceuticals, UCB Pharma; has served as a consultant to Merck & Co, Inc, GlaxoSmithKline, Pfizer Inc, AstraZeneca Pharmaceuticals LP, Allergan Inc, Ortho-McNeil, and Aradigm Corp; and has received an educational grant from GlaxoSmithKline. Dr Kudrow has been on a speaker's bureau of GlaxoSmithKline and Ortho-McNeil and has received grant and research support from Ortho-McNeil, GlaxoSmithKline, Pozen, Merck & Co, Inc, and Eisai Inc. Dr Fairclough received financial support as a consultant to perform analyses of the data in this study. Drs Rupnow and Greenberg are fulltime employees of Johnson & Johnson. Dr Rothrock has served as a paid consultant to Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pozen, and Allergan Inc; has received research support from those companies and from Abbott Laboratories, Elan Corporation, Esai Inc, and AstraZeneca Pharmaceuticals LP; and has received honoraria for lecturing from Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Elan Corporation, and Endo Pharmaceuticals.
Silberstein, 2007[30]	Industry	Yes	Yes	Yes	Dr. Silberstein has received personal compensation for activities with: GlaxoSmith-Kline, Inc., Johnson & Johnson, Merck & Co., Inc., UCB Pharma, AstraZeneca Pharmaceuticals, Inc., Pfizer, Inc., Allergan, Inc., Pozen, Inc., Abbott Laboratories, Inc., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					capacity for CurrentPain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Inc., Johnson & Johnson, Merck&Co., Inc., Pfizer, Inc., Allergan, Inc., and Abbott Laboratories, Inc. Dr. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan,Inc., Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil, Pfizer, Pozen, among other companies. Dr. Dodick has received personal compensation for activities with Allergan, Inc., GlaxoSmith-Kline, Inc., Pfizer, Inc., Endo Pharmaceuticals, Ortho-McNeil Pharmaceutical, Inc., Merck & Co., Inc., Medtronic, Neuralieve; has received personal compensation in an editorial capacity for Headache Currents; and has received research support from St. Jude, Allergan, Inc., Medtronic, Inc., National Institutes of Health, Mayo Clinic College of Medicine, and Advanced Bionics. Dr. Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer, Inc., and GlaxoSmithKline, Inc., and has received research support from Alzyer, AstraZeneca Pharmaceuticals, Inc., GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Precision, Division of Boston Scientific, Solvay S.A., and Vernalis. Dr. Ramadan has received personal compensation for activities with GlaxoSmithKline, Inc., Ortho- McNeil Neurologics, Inc., Eli Lilly & Company, Eisai, Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Pfizer, Inc., Merck & Co., Inc., Aradign Corp., Boehringer Ingelheim Pharmaceuticals and Map Pharmaceuticals; has received personal compensation in an editorial capacity for Web Alert; and has received research support from Ortho-McNeil Neurologics, Eli Lilly&Company, Pfizer, Inc., and the National Headache Ambassador Program. Dr. Mathew has received personal compensation for

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					activities with Eisai. Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, UCB Pharma, Allergan, Johnson & Johnson, AstraZeneca, Pfizer, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Novartis, Endo, Pozen, Inc., Vernalis, Ortho-McNeil, Advanced Bionics; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Pfizer, Merck, Ortho-McNeil, Allergan, MedPointe Pharmaceuticals, Endo, UCB Pharma; has served as a consultant to Merck, GlaxoSmith-Kline, Pfizer, AstraZeneca, Allergan, Ortho-McNeil, Aradigm Corporation; and has received educational funding from GlaxoSmithKline. Dr. Bigal has received personal compensation for activities from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, UCB, AstraZeneca, Pfizer, Inc., and Advance PCS and has received research support from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, Pfizer, UCB, AstraZeneca, and Advance PCS. Dr. Saper has received honoraria for speaking from GlaxoSmithKline, Merck & Co., Inc., Abbott Laboratories, Inc., Elan Corporation, AstraZeneca Pharmaceuticals, Pfizer, Inc., Ortho-McNeil Pharmaceuticals, Bristol-Myers Squibb, Medtronic, Inc., Endo Pharmaceuticals, Advanced Bionics, Pozen, Inc., and Penwest Pharmaceuticals Co; has received personal compensation in an editorial capacity for Pain Watch and Migraine Monitor; holds stock in Pozen, Inc.; and has received research support from Novartis, Ortho-McNeil Pharmaceuticals, Merck & Co., Inc., GlaxoSmithKline, Allergan, Inc., Eisai, Inc., AstraZeneca Pharmaceuticals, Abbott, Advanced Bionics, Medtronic, Renovis, and Pozen, Inc.Dr. Ascher is an employee of Ortho-McNeil Janssen Scientific Affairs, LLC. Dr. Jordan is an employee of PriCara, a Unit of Ortho-McNeil, Inc. Drs. Greenberg and Joseph Hulihan are employees of Ortho-McNeil Neurologics.

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
Lofland, 2007[31]	Industry	Yes	Yes	Yes	Jennifer H. Lofland received grant from Ortho-McNeil Janssen, Inc
Limmroth, 2007[32]	Industry	Yes	Yes	Yes	Volker Limmroth received honoraria as speaker from Janssen-Cilag, Germany. Susanne Schwalen is an employee of Janssen-Cilag, Germany
Diener, 2007[33]	Industry	Not reported	Not reported	Yes	JC Van Oene, M Lahaye and S Schwalen are employess of Janssen-Cilag
Lainez, 2007[34]	Not reported	Yes	Yes	Yes	Miguel JA La´ inez has received personal compensation or research support from activities with Allergan, Inc., Almirall SA, GlaxoSmithKline, Inc Jansen Cilag, Inc., Menarini, Merck & Co., Inc, Medtronic and Pfizer Inc. Frederick Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals,., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer Inc, and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Advanced Bionics, Solvay S.A., and Vernalis. Joop Pfeil is a paid consultant for Janssen Pharmaceutica/J & J, Novartis, Sanofi-Aventis, Pfizer, Schering-Plough, Numico, Vitatron, Actelion Pharmaceuticals and Sankyo. S. Ascher is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. W.H. Olson is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. S. Schwalen is a full-time employee of Janssen-Cilag GmbH.
Freitag, 2007[35]	Industry	Yes	Yes	Yes	Dr. Freitag has received honoraria, consulting fees, and research grant funds in excess of $10,000 per year from Johnson & Johnson and Ortho-McNeil Neurologics. Dr. Forde has received honoraria in excess of $10,000 per year from Johnson & Johnson and Ortho-McNeil Neurologics. Drs. Neto and Wang and Ms Schmitt are paid employees of Johnson & Johnson. Drs. Wu and Hulihan are paid employees of Ortho-McNeil Neurologics.
Dahlof, 2007[36]	Industry	Yes	Yes	Yes	Professor Carl Dahlöf has been a consultant/scientific advisor on advisory boards, clinical trials, and

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					investigator-initiated trials and a speaker for: Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Janssen Cilag, Merck, Lilly, NMT Medical Inc., Novartis, Ortho-McNeil Pharmaceutical, Pharmacia, Pfizer, Pierre Fabre, and St Jude Medical EMEAC. Elizabeth Loder has had no financial relationship with any pharmaceutical company since July 2006, except grant support from NMT for a clinical trial. She has been a speaker, received grant support, or been a consultant for: OrthoMcNeil, Endo, AstraZeneca, GlaxoSmithKline, Pfizer, and Allergan. She serves on the Board of Directors of the American Headache Society, the Executive Council of the International Headache Society, and the Board of the Headache Cooperative of New England. Merle Diamond has served as a consultant and/or conducted research with AstraZeneca, Ortho-McNeil Neurologies, GlaxoSmithKline, Merck and Co., Pfizer, and Primary Care Network. Marcia Rupnow is a full-time salary employee of Ortho-McNeil Janssen Scientific Affairs, LLC. George Papadopoulos was an employee of J&J Pharmaceutical Services at the time of study completion. Lian Mao is a full-time salary employee of Ortho-McNeil Janssen Scientific Affairs, LLC.
Diener, 2007[37]	Industry	Yes	Yes	Yes	Hans-Christoph Diener, Reto Agosti, Gianni Allais, Gennaro Bussone, Brendan Davies, Michel Lanteri-Minet, Mustafa Ertas, Uwe Reuter, Margarita Sanchez Del Rio, and Jean Schoenen have participated in clinical trials and advisory boards for Janssen-Cilag. Paul Bergmans, Susanne Schwalen, Joop van Oene are employees of Janssen-Cilag EMEA (Europe, Middle East, and Africa). Hans -Chirstoph Diener has received honoraria from Addex Pharmaceuticals, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid Pharmaceuticals, Böhringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Eli Lilly, F Hoff mann-La Roche, 3M Medica, Merck Sharp and Dohme, Novartis Pharmaceuticals, Johnson and Johnson,

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					Pierre Fabre, Pfi zer, Schaper and Brümmer, Sanofi - Aventis, and Weber and Weber, and fi nancial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfi zer.
Dodick, 2007[38]	Industry	Yes	Yes	Yes	David W. Dodick is a consultant/advisor for Eli Lilly, Glaxo-SmithKline, Merck, Neuralieve, Ortho-McNeil. He is involved in research studies with Advanced Bionics, AstraZeneca, Medtronic, and Alexza, for which his academic institution has received research grants.He is also the principal investigator of a multicenter clinical trial with St. Jude. He has no stock or equity in any pharmaceutical company. Stephen Silberstein has received personal compensation for activities with GlaxoSmithKline, Inc.; Johnson & Johnson; Merck & Co., Inc.; UCB Pharma; AstraZeneca Pharmaceuticals; Pfizer Inc.; Allergan, Inc.; Pozen, Inc.; Abbott Laboratories, Inc.; Eli Lilly & Company; NPS; and Xcel Pharmaceuticals. Dr. Silberstein has received personal compensation in an editorial capacity for Current Pain and Headache. Dr. Silberstein has received financial support for scholarly activities from GlaxoSmithKline, Inc.; Johnson & Johnson; Merck & Co., Inc.; Pfizer Inc.; Allergan, Inc.; and Abbott Laboratories, Inc. Joel Saper has received honoraria for speaking from Glaxo-SmithKline; Merck & Co., Inc.; Abbott Laboratories, Inc.; Elan Corporation; AstraZeneca Pharmaceuticals; Pfizer Inc.; Ortho-McNeil Pharmaceuticals, Inc.; Bristol-Myers Squibb; Medtronic Inc.; Endo Pharmaceuticals; Advanced Bionics; Pozen, Inc.; and Penwest Pharmaceuticals Co. Dr. Saper has received personal compensation in an editorial capacity for PainWatch and Migraine Monitor.He holds stock in Pozen, Inc. and has received research support from Novartis; Ortho-McNeil Pharmaceuticals, Inc; Merck & Co., Inc.; GlaxoSmith-Kline; Allergan, Inc.; Eisai Inc.; AstraZeneca Pharmaceuticals; Abbott; Advanced Bionics; Medtronic; Renovis; and Pozen,Inc. Fred G. Freitag has received personal compensation for

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					activities with Allergan, Inc.; AstraZeneca Pharmaceuticals; Merck & Co., Inc.; Ortho-McNeil Pharmaceuticals, Inc.;Valeant Pharmaceuticals International; Pfizer Inc.; and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer; AstraZeneca Pharmaceuticals; GlaxoSmithKline, Inc.; Merck & Co., Inc.; Ortho-McNeil Pharmaceuticals, Inc.; Advanced Bionics; Solvay S.A.; and Vernalis. Roger K. Cady has received personal compensation for activities with Allergan; Atrix Labs; Capnia; Endo; GlaxoSmith-Kline; Johnson & Johnson; Med Point; Merck; Ortho-McNeil Pharmaceuticals, Inc.; and Winston Labs. Dr. Cady received compensation from NIPC for serving as a co-editor of their migraine newsletter. Dr. Cady has received research support from Abbott; Allergan; Alexa; Aradigm Corp; Capnia; Cipher; Eisai Pharmaceuticals; Endo Pharmaceuticals; GelStat; Glaxo-SmithKline; Johnson & Johnson; Matrixx; Merck; Ortho-McNeil Pharmaceuticals, Inc.; Pfizer Inc.; and Vernalis. Alan M. Rapoport has received personal compensation from the following pharmaceutical companies, advisory boards, speaker's bureau, research or educational grants:Abbott Laboratories; Allergan, Inc.; AstraZeneca; Eisai Pharmaceuticals; Endo Pharmaceuticals; Forest Laboratories; GlaxoSmithKline; Endo Pharmaceuticals; Forest Laboratories; GlaxoSmithKline; Merck; Ortho-McNeil Pharmaceuticals, Inc.; Pfizer Inc.; UCB Pharma;Valeant;Vernalis; and Winston. Ninan T. Mathew has received personal compensation for activities with Eisai Pharmaceuticals. Joseph Hulihan, Concetta Crivera, Marcia F.T. Rupnow, Lian Mao, Gary Finlayson, and Steven J. Greenberg are employees of Ortho-McNeil Janssen Scientific Affairs, LLC.
Adelman, 2008[39]	Industry	Yes	Yes	Yes	James Adelman: Clinical Trials 1998–2006 (Ortho-McNeil Pharmaceuticals), Advisory Boards (Ortho-McNeil Pharmaceuticals), Speaker (Ortho-McNeil

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					Pharmaceuticals); Frederick Freitag: Consultant, honoraria recipient (OrthoMcNeil Pharmaceuticals and Ortho-McNeil Neurologics), research grant recipient (Johnson and Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals, and Ortho-McNeil Neurologics); Miguel Lainez: grant/research recipient, consultant/scientific advisor, honoraria recipient (Allergan, Almirall Prodesfarma, Boehringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen Cilag, Johnson and Johnson, MSD, Novartis, Pierre Fabre, and Sanofi-Synthelabo).
Silberstein, 2009[40]	Industry	Yes	Yes	Yes	Stephen Silberstein has received personal compensation for activities with: Johnson & Johnson, GlaxoSmith-Kline, Merck, UCB Pharma, AstraZeneca, Pfizer, Allergan, Pozen, Abbott Laboratories., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial capacity for Current Pain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Allergan, and Abbott Laboratories. Richard B. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeill, Pfizer, and Pozen, among other companies. David W. Dodick has served as a consultant for GlaxoSmithKline, Merck, Allergan, Endo, Pfizer, Eli Lilly, Addex, Solvay, and Neuralieve and has received research support from Advanced Neurostimulation Systems, Medtronic, and St. Jude. Fred Freitag has received grants and research support from Advanced Bionics Corporation, Alzyer, AstraZeneca, CAPNIA, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Solvay, and Vernalis Pharmaceuticals.He has served as a consultant for Allergan,AstraZeneca,CAPNIA, Endo Pharmaceuticals, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, and

Appendix Table 20. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
					Valeant Pharmaceuticals International. He has served on the speakers bureaus of AstraZeneca, GlaxoSmithKline, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Pfizer, and Valeant Pharmaceuticals International. Ninan Mathew has received personal compensation for activities involving continuing medical education and for advisory board participation from Ortho McNeil, Merck, Allergan, GlaxoSmithKline, Endo, and Valiant. Jan Brandes has received grants, research support, or served as a consultant to Merck, GlaxoSmithKline, UCB Pharma, Pfizer, Allergan, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan, Novartis, Endo, Pozen,Vernalis, Ortho-McNeil, Advanced Bionics, MedPointe, and Aradigm. Marcelo E. Bigal is a full-time employee of Merck Research Laboratories.This manuscript was written during his tenure at the Albert Einstein College of Medicine.He has received, in the past, compensation from Ortho-McNeil Pharmaceutical,AstraZeneca, GlaxoSmithKline, Merck, Allergan, MAP, NMT, and Endo, among other pharmaceutical companies. Steve Ascher, Jacqueline D. Morein, and Pamela Wright are employees of Ortho-McNeil Janssen Scientific Affairs, LLC. Steven J. Greenberg is an employee of EMD Serono Inc.
Lipton, 2011[41]	Industry	Yes	Yes	Yes	Not reported, however, David Biondi, Steven Ascher, William Olson and Joseph Hulihan were from Ortho-McNeil Janssen Scientific Affairs, USA

Appendix Table D21. Risk of bias in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	Masking of treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Storey, 2001[17]	Double-blind	No	Unclear	Yes (Topiramate group had no men and higher number of patients with concurrent preventative treatment),but the differences were not significant	Unclear	Low
Edwards, 2003[18]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
Silvestrini, 2003[19]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2003[20]	Double-blind	No	Unclear	Yes	Unclear	Moderate
Brandes, 2004[21]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Silberstein, 2004[22]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mei, 2004[23]	Double-blind	No	Unclear	Unclear	Unclear	Moderate
Bussone, 2005[24]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diamond, 2005[25]	Double-blind	Yes	Unclear	Previously reported[21, 22, 42]	Unclear	Low
Silberstein, 2006[26]	Double-blind	Yes	Unclear	Not adequate. Topiramate 200mg/day group has lower % of women and higher % of men as compared to other groups, but the differences were not significant (previously reported)	Unclear	Moderate
Mei, 2006[27]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[28]	Double-blind	Yes	Unclear	Not reported	Unclear	Moderate
Brandes, 2006[29]	Double-blind	Yes	Clearly adequate	Not adequate; the % of male patients were much lower in the topiramate100mg and 200mg groups, but the difference were not significant	Unclear	Moderate
Silberstein, 2007[30]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Lofland, 2007[31]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Limmroth, 2007[32]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[33]	Double-blind	Yes	Unclear	Not adequate (Mean Beck Depression Inventory scores were higher in	Unclear	Moderate

Appendix Table 21. Risk of bias in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Masking of treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
				placebo as compared to topiramate),but the differences were not significant		
Lainez, 2007[34]	Double-blind	No	Unclear	Yes	Unclear	Low
Freitag, 2007[35]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Dahlof, 2007[36]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[37]	Double-blind	Yes	Unclear	Yes	Unclear	Moderate
Dodick, 2007[38]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Adelman, 2008[39]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2009[40]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Lipton, 2011[41]	Double-blind	Yes	Unclear	Yes	The study mentions the significance of the outcome: ≥50% and 75% reduction in headache days and migraine headache days, however, the results are not given	Low

Appendix Table D22. Strength of evidence of migraine prevention with topiramate in adults

Outcomes	Daily topiramate dose	Reference, Sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
≥50% reduction in monthly migraine days	100 mg/day	Bussone, 2005[24]	Low				
	100 mg/day	Silberstein, 2009[40]	Low				
	50 to 200mg/day	Diener, 2007[33]	Moderate				
	50 to 200mg/day	1145	Low	Yes	Yes	Yes	High
≥75% reduction in monthly migraine attack rate	100 mg/day	Bussone, 2005[24]	Low				
	100 mg/day	Silberstein, 2009[40]	Low				
	50mg/day	Silvestrini, 2003[19]	Low				
	200mg/day	Silberstein, 2006[28]	Moderate				
		1327	Low	Yes	Yes	Yes	High
	100 mg/day	Silberstein, 2009[40]	Low				
	100 mg/day	Bussone, 2005[24]	Low				
		328	Low	Yes	Yes	No	Moderate
At least 50% reduction in monthly migraine frequency (responder rate)	100 mg/day	Brandes, 2004[21]	Low				
	100 mg/day	Mei, 2004[23]	Moderate				
	100 mg/day	Silberstein, 2004[22]	Low				
	100 mg/day	Silberstein, 2009[40]	Low				
		774	Low	Yes	Yes	Yes	High
	200mg/day	Brandes, 2004[21]	Low				
	200mg/day	Silberstein, 2003[20]	Moderate				
	200mg/day	Silberstein, 2004[22]	Low				
	200mg/day	Silberstein, 2006[28]	Moderate				
	200mg/day	Edwards, 2003[18]	Low				
		746	Low	Yes	Yes	Yes	High
	50mg/day	Brandes, 2004[21]	Low				
	50mg/day	Silberstein, 2003[20]	Moderate				
	50mg/day	Silberstein, 2004[22]	Low				
	50mg/day	Silvestrini, 2003[19]	Low				
		507	Low	Yes	Yes	Yes	High
Complete cure	100 mg/day	Freitag, 2007[35]	Low				
	200mg/day	Silberstein, 2006[28]	Moderate				
	50mg/day	Silvestrini, 2003[19]	Low				
	100 mg/day	Silberstein, 2009[40]	Low				
		893	Low	Yes	Yes	No	Moderate

Appendix Table D23. Migraine prevention with topiramate vs. placebo in adults (pooled results from randomized controlled clinical trials)

Outcome	Reference, Sample	Daily dose	Events/ randomized, Rate with drug	Events/ randomized, Rate with placebo	Relative risk (95% CI)	Weight	Absolute risk difference, (95% CI)	Weight, random effects inverse variance	Absolute risk difference, (95% CI)	Weight, Maximum likelihood
≥50% reduction in monthly migraine days	Bussone, 2005[24]	100 mg/day	175/386 50%	81/372 20%	2.1 (1.7 to 2.6)	51.03	0.24 (0.17 to 0.30)	42.39	0.22 (0.17 to 0.28)	42.5
	Silberstein, 2009[40]	100 mg/day	62/165 40%	47/163 30%	1.3 (1.0 to 1.8)	46.19	0.09 (-0.01 to 0.19)	33.8	0.12 (0.04 to 0.20)	33.8
	Diener, 2007[33]	50 to 200mg/day	7/32 20%	0/27 0%	12.7 (0.8 to 213.1)	2.78	0.22 (0.07 to 0.37)	23.81	0.20 (0.10 to 0.30)	23.7
Overall	**1145**		**244/583 41.80%**	**128/562 22.80%**	**1.8 (1.1 to 2.9)**	**100**	**0.18 (0.08 to 0.28)**	**100**	**0.18 (0.09 to 0.27)**	**100**
≥75% reduction in monthly migraine attack rate	Bussone, 2005[24]	100 mg/day	108/386 30%	50/372 10%	2.1 (1.5 to 2.8)	81.08	0.15 (0.09 to 0.20)	30.99	0.15 (0.09 to 0.20)	31
	Silberstein, 2009[40]	100 mg/day	9/165 10%	6/163 0%	1.5 (0.5 to 4.1)	7.32	0.02 (-0.03 to 0.06)	32.16	0.02 (-0.02 to 0.07)	32.2
	Silvestrini, 2003[19]	50mg/day	6/14 40%	0/14 0%	13.0 (0.8 to 210.8)	0.96	0.43 (0.16 to 0.70)	10.02	0.28 (0.10 to 0.47)	10
	Silberstein, 2006[28]	200mg/day	27/140 20%	6/73 10%	2.3 (1.0 to 5.4)	10.63	0.11 (0.02 to 0.20)	26.83	0.12 (0.03 to 0.20)	26.8
Overall	**1327**		**150/705 21.20%**	**62/622 9.90%**	**2.1 (1.6 to 2.8)**	**100**	**0.12 (0.02 to 0.22)**	**100**	**0.14 (0.02 to 0.26)**	**100**
≥75% reduction in monthly migraine days	Silberstein, 2009[40]	100 mg/day	25/165 20%	15/163 10%	1.6 (0.9 to 3.0)	23.68	0.06 (-0.01 to 0.13)	46.21	0.08 (0.02 to 0.13)	46.2
	Bussone, 2005[24]	100 mg/day	98/386 30%	41/372 10%	2.3 (1.6 to 3.2)	76.32	0.14 (0.09 to 0.20)	53.79	0.13 (0.09 to 0.18)	53.8
Overall	**328**		**25/165 15.20%**	**15/163 9.20%**	**2.1 (1.6 to 2.9)**	**100**	**0.11 (0.02 to 0.19)**	**100**	**0.11 (0.04 to 0.17)**	**100**
At least 50% reduction in monthly migraine frequency (responder rate)	Brandes, 2004[21]	100 mg/day	60/122 50%	9/40.33 20%	2.2 (1.2 to 4.0)	22.66	0.27 (0.11 to 0.42)		0.26 (0.12 to 0.39)	24.2
	Mei, 2004[23]	100 mg/day	37/58 60%	12/57 20%	3.0 (1.8 to 5.2)	24.71	0.43 (0.27 to 0.59)		0.37 (0.24 to 0.51)	23.9
	Silberstein, 2004[22]	100 mg/day	69/128 50%	9/40.48 20%	2.4 (1.3 to 4.4)	22.84	0.31 (0.16 to 0.47)		0.30 (0.17 to 0.43)	24.3
	Silberstein, 2009[40]	100 mg/day	43/165 30%	35/163 20%	1.2 (0.8 to 1.8)	29.8	0.05 (-0.05 to 0.14)		0.07 (-0.02 to 0.16)	27.6
Overall	**774**		**208/473 44.10%**	**65/300.81 21.70%**	**2.0 (1.3 to 3.2)**	**100**	**0.26 (0.07 to 0.44)**	**110**	**0.25 (0.10 to 0.40)**	**100**

Appendix Table 23. Migraine prevention with topiramate vs. placebo in adults (pooled results from randomized controlled clinical trials) (continued)

Outcome	Reference, Sample	Daily dose	Events/ randomized, Rate with drug	Events/ randomized, Rate with placebo	Relative risk (95% CI)	Weight	Absolute risk difference, (95% CI)	Weight, random effects inverse variance	Absolute risk difference, (95% CI)	Weight, Maximum likelihood
At least 50% reduction in monthly migraine frequency (responder rate)	Brandes, 2004[21]	200mg/day	57/121 50%	9/40 20%	2.1 (1.1 to 3.8)	21.15	0.25 (0.09 to 0.40)	20.32	0.23 (0.12 to 0.35)	20.3
	Silberstein, 2003[20]	200mg/day	58/112 50%	8/36.38 20%	2.3 (1.2 to 4.4)	20.2	0.30 (0.13 to 0.46)	19.44	0.26 (0.14 to 0.38)	19.4
	Silberstein, 2004[22]	200mg/day	61/117 50%	8/37 20%	2.4 (1.3 to 4.6)	20.18	0.31 (0.15 to 0.47)	19.89	0.26 (0.15 to 0.38)	19.7
	Silberstein, 2006[28]	200mg/day	55/140 40%	25/73 30%	1.1 (0.8 to 1.7)	28.96	0.05 (-0.09 to 0.19)	23.13	0.12 (0.01 to 0.22)	23.4
	Edwards, 2003[18]	200mg/day	12/34 40%	3/36 10%	4.2 (1.3 to 13.7)	9.5	0.27 (0.09 to 0.45)	17.22	0.25 (0.12 to 0.37)	17.2
Overall	**746**		**243/524 46.40%**	**54/222.38 24.20%**	**2.0 (1.3 to 3.0)**	**100**	**0.23 (0.12 to 0.33)**	**100**	**0.22 (0.12 to 0.33)**	**100**
At least 50% reduction in monthly migraine frequency (responder rate)	Brandes, 2004[21]	50mg/day	47/120 40%	9/39.67 20%	1.7 (0.9 to 3.2)	32.23	0.17 (0.01 to 0.32)	27.06	0.17 (0.03 to 0.32)	27
	Silberstein, 2003[20]	50mg/day	41/117 40%	9/38.01 20%	1.5 (0.8 to 2.8)	31.82	0.11 (-0.05 to 0.27)	26.75	0.14 (-0.01 to 0.29)	26.9
	Silberstein, 2004[22]	50mg/day	45/125 40%	9/39.53 20%	1.6 (0.9 to 3.0)	31.9	0.14 (-0.02 to 0.29)	27.19	0.15 (0.01 to 0.29)	27.2
	Silvestrini, 2003[19]	50mg/day	10/14 70%	1/14 10%	10.0 (1.5 to 68.0)	4.04	0.64 (0.37 to 0.92)	19	0.51 (0.29 to 0.74)	19
Overall	**507**		**143/376 37.90%**	**28/131.21 21.20%**	**1.7 (1.2 to 2.6)**	**100**	**0.23 (0.06 to 0.41)**	**100**	**0.24 (0.05 to 0.44)**	**100**
Complete cure	Freitag, 2007[35]	100 mg/day	14/245 10%	2/79.02 0%	2.3 (0.5 to 9.7)	38.52	0.03 (-0.01 to 0.08)	30.59	0.03 (-0.01 to 0.08)	30.6
	Silberstein, 2006[28]	200mg/day	10/140 10%	2/73 0%	2.6 (0.6 to 11.6)	36.89	0.04 (-0.01 to 0.10)	26.04	0.05 (-0.01 to 0.10)	26
	Silvestrini, 2003[19]	50mg/day	4/14 30%	0/14 0%	9.0 (0.5 to 152.9)	10.23	0.29 (0.04 to 0.54)	3.09	0.14 (0.00 to 0.28)	3.1
	Silberstein, 2009[40]	100 mg/day	1/165 0%	2/163 0%	0.5 (0.0 to 5.4)	14.36	-0.01 (-0.03 to 0.01)	40.27	-0.01 (-0.03 to 0.02)	40.3
Overall	893		29/564 5.20%	6/329.02 1.70%	2.2 (0.9 to 5.5)	100	0.03 (-0.02 to 0.07)	100	0.05 (-0.02 to 0.13)	100

Bold- significant at 95% connfidence limit
CI – confidence interval

Appendix Table D24. Reduction in migraine frequency and duration in randomized controlled clinical trials that examined efficacy of topiramate in adults

Definition of the outcome	Reference Risk of bias	Mean [standard deviation] with drug	Daily dose	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandardized mean difference (95% CI)
Mean monthly migraine days	Silberstein, 2004[22] Risk of bias Low	3.7 [3.3]	100 mg/day	5.3 [3.6]	-0.4 (-6.7 to -4.2)	-1.6 (-2.5 to -0.7)
Mean monthly migraine days	Mei, 2006[27] Risk of bias Low	3.1 [0.91]	100 mg/day	15.4 [4.38]	-4.3 (-5.3 to -3.3)	-12.2 (-14.2 to -12.3)
Mean monthly migraine days	Brandes, 2006[29] Risk of bias Moderate	3.5 [3.5]	100 mg/day	4.5 [2.9]	-0.3 (-1.6 to -0.1)	-1.0 (-1.8 to -0.2)
Pooled with random effects	**Risk of bias**	**Low**	**100 mg/day**		**-1.4 (-2.5 to -7.4)**	**-4.8 (-9.4 to -3.2)**
Mean monthly migraine days	Silvestrini, 2003[19] Risk of bias Low	8.1 [8.3]	50mg/day	20.6 [4.4]	-1.8 (-2.8 to -1.8)	-12.5 (-17.4 to -7.6)
Mean monthly migraine days	Silberstein, 2004[22] Risk of bias Low	4.8 [4]	50mg/day	5.3 [3.6]	-0.1 (-3.4 to 1.1)	-0.5 (-1.5 to 0.5)
Pooled with random effects	Risk of bias	Low	50mg/day		-0.9 (-2.7 to 5.8)	-6.2 (-18.5 to 5.5)
Mean reduction in the monthly number of migraine days	Brandes, 2004[21] Risk of bias Low	-2.6 [3.4]	100 mg/day	-1.3 [3.5]	-0.3 (-7.6 to -5.1)	-1.3 (-2.2 to -0.4)
Mean reduction in the monthly number of migraine days	Silberstein, 2007[30] Risk of bias Low	-6.4 [5.8]	100 mg/day	-4.7 [6.1]	-0.2 (-8.5 to -6.1)	-1.7 (-3.0 to -0.4)
Mean reduction in the monthly number of migraine days	Lipton, 2011[41] Risk of bias Low	-6.6 [3.5]	100 mg/day	-5.3 [3.6]	-0.3 (-6.6 to -6.2)	-1.3 (-2.0 to -0.6)
Mean reduction in the monthly number of migraine days	Brandes, 2004[21] Risk of bias Low	-2.9 [3.41]	200mg/day	-1.3 [3.51]	-0.4 (-6.7 to -2.2)	-1.6 (-2.5 to -0.7)
Mean reduction in the monthly number of migraine days	Diener, 2007[33] Risk of bias Moderate	-3.5 [6.3]	50 to 200mg/day	0.2 [4.7]	-0.6 (-1.2 to -6.1)	-3.7 (-6.5 to -0.9)
Pooled with random effects	**Risk of bias**	**Low**	**50 to 200mg/day**		**-0.3 (-7.5 to -8.3)**	**-1.4 (-1.9 to -1.8)**
Monthly migraine frequency	Silberstein, 2004[22] Risk of bias Low	4.1 [3.6]	50mg/day	4.6 [3]	-0.1 (-5.4 to 0.1)	-0.5 (-1.3 to 0.3)
Monthly migraine frequency	Brandes, 2006[29] Risk of bias Moderate	4.1 [3.6]	50mg/day	4.5 [2.9]	-0.1 (-2.4 to 2.1)	-0.4 (-1.2 to 0.4)
Pooled with random effects	Risk of bias	Moderate	50mg/day		-0.1 (-3.3 to 7.0)	-0.4 (-1.5 to 1.1)

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D25. Reduction in migraine severity and symptoms in randomized controlled clinical trials that examined efficacy of topiramate in adults

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard Mean difference (95% CI)
Storey, 2001[17] Risk of bias Low	Mean migraine severity during treatment	200mg/day	19 [21]	2.0 [0.4]	2.0 [0.4]	-0.1 (-0.7 to 0.5)	0.0 (-0.3 to 0.2)
Silberstein, 2009[40] Risk of bias Low	Mean change in the rating of average daily headache severity	100 mg/day	165 [163]	-0.3 [0.6]	-0.2 [0.4]	-0.2 (-0.4 to 0.0)	-0.1 (-0.2 to 0.0)
	Change in worst daily headache severity	**100 mg/day**	**165 [163]**	**-0.4 [0.7]**	**-0.2 [0.5]**	**-0.3 (-0.5 to -0.1)**	**-0.2 (-0.3 to -0.1)**
	Mean decrease from baseline in the severity of nausea, photophobia, and phonophobia	100 mg/day	165 [163]	-0.2 [0.5]	-0.1 [0.4]	-0.2 (-0.4 to 0.0)	-0.1 (-0.2 to 0.0)
	Mean change from baseline in the monthly frequency of nausea	100 mg/day	165 [163]	-3.4 [5.8]	-2.3 [5.7]	-0.2 (-0.4 to 0.0)	-1.1 (-2.3 to 0.1)
	Mean change from baseline in the monthly rate of vomiting	100 mg/day	165 [163]	-1.0 [2.1]	-0.7 [2.6]	-0.1 (-0.3 to 0.1)	-0.3 (-0.8 to 0.2)
	Mean change from baseline in the monthly frequency of photophobia	100 mg/day	165 [163]	-5.0 [6.4]	-3.8 [5.6]	-0.2 (-0.4 to 0.0)	-1.2 (-2.5 to 0.1)
	Mean change from baseline in the monthly frequency of phonophobia	100 mg/day	165 [163]	-5.2 [6.0]	-3.6 [6.2]	-0.3 (-0.5 to 0.0)	-1.6 (-2.9 to -0.3)

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D26. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
Silberstein, 2009[40] Risk of bias Low	**Mean change from baseline in the headache index (The headache index was calculated as the sum of the product of daily average headache severity multiplied by headache duration for the day, divided by the number of days in the specified period)**	**100 mg/day**	**165 [163]**	**-0.3 [0.3]**	**-0.2 [0.4]**	**-0.3 (-0.5 to -0.1)**	**-0.1 (-0.2 to 0.0)**
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire)scores: Emotional function domain	100 mg/day	165 [163]	-26.3 [27.8]	-21.0 [30.2]	-0.2 (-0.4 to 0.0)	-5.3 (-11.6 to 1.0)
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire) scores: Role Function Preventive domain	100 mg/day	165 [163]	-16.1 [21.5]	-12.6 [21.0]	-0.2 (-0.4 to 0.1)	-3.5 (-8.1 to 1.1)
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire) scores: Role Function Restrictive domain	100 mg/day	165 [163]	-23.7 [23.1]	-18.8 [22.6]	-0.2 (-0.4 to 0.0)	-4.9 (-9.8 to 0.0)
	Mean change from baseline in the MIDAS (Migraine Disability Assessment) score	100 mg/day	165 [163]	-31.4 [53.8]	-21.0 [52.2]	-0.2 (-0.4 to 0.0)	-10.4 (-21.9 to 1.1)
Diener, 2007[37] Risk of bias Moderate	**Mean change in HIT-6 (Headache Impact Test) questionnaire in the last 4 weeks of double-blind phase compared to open-label baseline**	**100mg/day**	**255 [259]**				**-1.9 (-3.4 to -0.4)**
	Mean change in SF-12 mental component score in the last 4 weeks of double-blind phase compared to open-label baseline	100mg/day	255 [259]				-1.2 (-3.4 to 1.0)
	Mean change in SF-12 physical health	100mg/day	255 [259]	-1.7	-3.1	NS	
	MIDAS score change at end-point	**50 to 200mg/day**	**32 [27]**	**-26.0 [61.0]**	**3.0 [21.0]**	**-0.6 (-1.1 to -0.1)**	**-29.0 (-51.6 to -6.4)**

Appendix Table 26. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
Brandes, 2006[29] Risk of bias Moderate	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	50mg/day	117 [114]	77.6 [22.71]	74.1 [21.35]	0.2 (-0.1 to 0.4)	3.5 (-2.2 to 9.2)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	**100 mg/day**	**120 [114]**	**82.9 [23.00]**	**74.1 [21.35]**	**0.4 (0.1 to 0.7)**	**8.8 (3.1 to 14.5)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	**200mg/day**	**117 [114]**	**82.7 [22.71]**	**74.1 [21.35]**	**0.4 (0.1 to 0.7)**	**8.6 (2.9 to 14.3)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	50mg/day	117 [114]	82.6 [18.39]	80.8 [17.08]	0.1 (-0.2 to 0.4)	1.8 (-2.8 to 6.4)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	**100 mg/day**	**120 [114]**	**85.5 [18.62]**	**80.8 [17.08]**	**0.3 (0.0 to 0.5)**	**4.7 (0.1 to 9.3)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	**200mg/day**	**117 [114]**	**87.2 [18.39]**	**80.8 [17.08]**	**0.4 (0.1 to 0.6)**	**6.4 (1.8 to 11.0)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: restrictive: at end of study	50mg/day	117 [114]	71.9 [20.55]	67.2 [19.22]	0.2 (0.0 to 0.5)	4.7 (-0.4 to 9.8)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating	**100 mg/day**	**120 [114]**	**75.8 [20.81]**	**67.2 [19.22]**	**0.4 (0.2 to 0.7)**	**8.6 (3.5 to 13.7)**

Appendix Table 26. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
	better functioning)-role function: restrictive: at end of study						
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: restrictive: at end of study	**200mg/day**	**117 [114]**	**77.9 [18.39]**	**67.2 [17.08]**	**0.6 (0.3 to 0.9)**	**10.7 (6.1 to 15.3)**
Silberstein, 2006[26] Risk of bias Moderate	**MSQ role function: prevention domain score at end point**	**100 mg/day**	**125 [115]**	**88.3 [15.7]**	**80.6 [16.1]**	**0.5 (0.2 to 0.7)**	**7.7 (3.7 to 11.7)**
	MSQ role function: prevention domain score at end point	200mg/day	112 [115]	84.4 [18.0]	80.6 [16.1]	0.2 (0.0 to 0.5)	3.8 (-0.6 to 8.2)
	MSQ role function: prevention domain score at end point	50mg/day	117 [115]	84.3 [16.2]	80.6 [16.1]	0.2 (0.0 to 0.5)	3.7 (-0.5 to 7.9)
	MSQ role function: restrictive domain score at end point	100 mg/day	125 [115]	77.2 [19.0]	65.8 [19.3]	0.6 (0.3 to 0.9)	11.4 (6.5 to 16.3)
	MSQ role function: restrictive domain score at end point	**200mg/day**	**112 [115]**	**75.8 [21.2]**	**65.8 [19.3]**	**0.5 (0.2 to 0.8)**	**10.0 (4.7 to 15.3)**
	MSQ role function: restrictive domain score at end point	**50mg/day**	**117 [115]**	**72.2 [19.5]**	**65.8 [19.3]**	**0.3 (0.1 to 0.6)**	**6.4 (1.4 to 11.4)**
	MSQ role function: emotional function score at end point	**100 mg/day**	**125 [115]**	**84.4 [21.2]**	**72.9 [21.4]**	**0.5 (0.3 to 0.8)**	**11.5 (6.1 to 16.9)**
	MSQ role function: emotional function score at end point	**200mg/day**	**112 [115]**	**81.2 [23.3]**	**72.9 [21.4]**	**0.4 (0.1 to 0.6)**	**8.3 (2.5 to 14.1)**
	MSQ role function: emotional function score at end point	**50mg/day**	**117 [115]**	**78.5 [21.6]**	**72.9 [21.4]**	**0.3 (0.0 to 0.5)**	**5.6 (0.1 to 11.1)**
Diamond, 2005[25] Risk of bias Low	**MSQ: Emotional domain: endpoint score**	**100 mg/day**	**384 [372]**	**82.5 [21.6]**	**73.5 [21.2]**	**0.4 (0.3 to 0.6)**	**9.0 (6.0 to 12.0)**
	MSQ: Prevention domain: endpoint score	**100 mg/day**	**384 [372]**	**85.5 [17.6]**	**79.9 [17.4]**	**0.3 (0.2 to 0.5)**	**5.6 (3.1 to 8.1)**
	MSQ: Restriction domain: endpoint score	**100 mg/day**	**384 [372]**	**75.4 [21.6]**	**66.5 [19.3]**	**0.4 (0.3 to 0.6)**	**8.9 (6.0 to 11.8)**

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D27. General health status in pooled analysis of individual patient data from randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (Medical Outcome Study Short Form 36 (SF-36) scores for each domain range from 0 to 100 with a higher score representing better function, a change of five points on the SF-36 is generally considered clinically meaningful)[36]

Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
SF-36: Bodily pain: change from baseline	**100 mg/day**	**384 [372]**	**11.5 [1.2]**	**4.6 [1.2]**	**5.8 (5.4 to 6.1)**	**6.9 (6.7 to 7.1)**
SF-36: General health: Change from baseline	**100 mg/day**	**384 [372]**	**2.2 [0.8]**	**0.8 [0.8]**	**1.8 (1.6 to 1.9)**	**1.4 (1.3 to 1.5)**
SF-36: Mental component summary: change from baseline	**100 mg/day**	**384 [372]**	**-0.2 [0.5]**	**0.1 [0.5]**	**-0.6 (-0.7 to -0.5)**	**-0.3 (-0.4 to -0.2)**
SF-36: Mental health: change from baseline	**100 mg/day**	**384 [372]**	**-0.5 [0.9]**	**-0.2 [0.9]**	**-0.3 (-0.5 to -0.2)**	**-0.3 (-0.4 to -0.2)**
SF-36: Physical component summary: change from baseline	**100 mg/day**	**384 [372]**	**4.7 [0.4]**	**2.5 [0.4]**	**5.5 (5.2 to 5.8)**	**2.2 (2.1 to 2.3)**
SF-36: Physical functioning: change from baseline	**100 mg/day**	**384 [372]**	**5.3 [0.8]**	**3.6 [0.9]**	**2.0 (1.8 to 2.2)**	**1.7 (1.6 to 1.8)**
SF-36: Role-emotional: change from baseline	**100 mg/day**	**384 [372]**	**2.3 [2.0]**	**3.0 [2.0]**	**-0.4 (-0.5 to -0.2)**	**-0.7 (-1.0 to -0.4)**
SF-36: Role-physical: change from baseline	**100 mg/day**	**384 [372]**	**17.9 [2.1]**	**12.0 [2.1]**	**2.8 (2.6 to 3.0)**	**5.9 (5.6 to 6.2)**
SF-36: Social functional: change from baseline	100 mg/day	384 [372]	4.8 [1.2]	4.8 [1.2]	0.0 (-0.1 to 0.1)	0.0 (-0.2 to 0.2)
SF-36: Vitality: change from baseline	**100 mg/day**	**384 [372]**	**5.2 [1.0]**	**1.8 [1.0]**	**3.4 (3.2 to 3.6)**	**3.4 (3.3 to 3.5)**

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D28. Drug utilization for acute migraine attacks in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
Mei, 2006[27] Risk of bias Low	**Amount of acute medication taken monthly**	**100 mg/day**	**30 [20]**	**3.2 [1.0]**	**15.4 [4.4]**	**-4.2 (-5.2 to -3.2)**	**-12.2 (-14.2 to -10.3)**
Diener, 2007[33] Risk of bias Moderate	Change in number of days per month of acute medications intake	50 to 200mg/day	32 [27]	-3.0 [5.9]	-0.7 [6.2]	-0.4 (-0.9 to 0.1)	-2.3 (-5.4 to 0.8)
Silberstein, 2009[40] Risk of bias Low	Mean change from baseline in the number of days per month that subjects used acute headache medications	100 mg/day	165 [163]	-4.4 [5.8]	-3.4 [5.3]	-0.2 (-0.4 to 0.0)	-1.0 (-2.2 to 0.2)
Diener, 2007[37] Risk of bias Moderate	Mean change in intake of acute medication in the last 4 weeks of double-blind phase compared to open-label baseline	100mg/day	255 [259]				-1.0 (-1.5 to -0.4)
Silberstein, 2004[22] Risk of bias Low	**Mean monthly Acute rescue medications days during the double-blind phase**	**100 mg/day**	**128 [117]**	**4.0 [3.4]**	**5.2 [3.3]**	**-0.4 (-0.6 to -0.1)**	**-1.2 (-2.0 to -0.4)**
	Mean monthly Acute rescue medications days during the double-blind phase	50mg/day	125 [117]	4.5 [3.1]	5.2 [3.3]	-0.2 (-0.5 to 0.0)	-0.7 (-1.5 to 0.1)
Brandes, 2004[21] Risk of bias Low	**Mean reduction in the monthly number of days when acute rescue medications were used**	**100 mg/day**	**122 [120]**	**-2.1 [3.20]**	**-1.0 [3.18]**	**-0.3 (-0.6 to -0.1)**	**-1.1 (-1.9 to -0.3)**
	Mean reduction in the monthly number of days when acute rescue medications were used	**200mg/day**	**121 [120]**	**-2.2 [3.19]**	**-1.0 [3.18]**	**-0.4 (-0.6 to -0.1)**	**-1.2 (-2.0 to -0.4)**

Appendix Table 28. Drug utilization for acute migraine attacks in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of bias	Definition of the outcome	Daily dose	Subjects in active [control] groups	Mean [standard deviation] with drug	Mean [standard deviation] with placebo	Cohen mean difference (95% CI)	Nonstandard mean difference (95% CI)
Lipton, 2011[41] Risk of bias Low	**Number of days of acute medications use**	**100 mg/day**	**188 [197]**	**-4.8 [3.5]**	**-3.8 [3.7]**	**-0.3 (-0.5 to -0.1)**	**-1.0 (-1.7 to -0.3)**
Bussone, 2005[24] Risk of bias Low	**Percentage of migraine days with intake of medication to treat acute migraine attacks: from baseline to endpoint**	**100 mg/day**	**386 [372]**	**12.7 [0.6]**	**16.4 [0.6]**	**-6.7 (-7.1 to -6.4)**	**-3.7 (-3.8 to -3.6)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D29. Randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Active drug	Reference Sample Number analyzed % women	Definition of migraine % without aura	Baseline severity	Age of subjects (eligible and mean)	Years of migraine % with prior preventative treatment
Divalproex	Mathew, 1995[43] Sample 107 Analyzed 105 % of women 77.6	Migraine (International Headache Society) % without aura: 95	Days per 4 week with migraine headaches during baseline phase: 7	16-75 Mean: 45.6	Years of migraine: 25 % with prior treatment: NR
Divalproex	Freitag, 2002[44] Sample 239 Analyzed 237 % of women 79	Migraine (International Headache Society) % without aura: 97	Days per 4 week with migraine headaches during baseline phase: 6.1	≥ 12 Mean: 40.5	Years of migraine: 20.2 % with prior treatment: NR
Divalproex	Klapper, 1997[45] Sample 176 Analyzed 171 % of women 89	Migraine (International Headache Society) % without aura: NR	Migraine attacks impairing usual activities during baseline (4 weeks): 5.8	≥ 16 Mean: 40.8	Years of migraine: 21.6 % with prior treatment: 53
Valproate	Hering, 1992[46] Sample 32 Analyzed 29 % of women 79.3	Migraine with aura (classical); patients suffering from migraine without aura (common); Ad Hoc Committee on Classification of Headache. % without aura: 13.7 (assumed)	From inclusion criteria: at least four attacks per months	NR (range: 18-54) Mean: 34	Years of migraine: 14 % with prior treatment: NR
Valproate	Jensen, 1994[47] Sample 43 Analyzed 34 % of women 86	Diagnosis of migraine without aura (I.H.S.) % without aura: 100	Mean frequency of migraines (4 weeks): 6.6	18-70 Mean: 46	Years of migraine: NR % with prior treatment: NR

NR –Not reported

Appendix Table D30. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Active drug	Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Divalproex	Mathew, 1995[43]	Industry	Yes	Yes	Yes	One author is employed by Abbott Laboratory, study funder.
Divalproex	Freitag, 2002[44]	Industry	Yes	Yes	Yes	Three authors are employed by Abbott Laboratory, study funder.
Divalproex	Klapper, 1997[45]	Industry	NR	NR	Yes	Five study participants are employed by Abbott Laboratory, study funder.
Valproate	Hering, 1992[46]	NR	Yes	Yes	NR	NR
Valproate	Jensen, 1994[47]	Industry	Yes	Yes	NR	NR

NR –Not reported

Appendix Table D31. Risk of bias in randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Reference	Masking of treatment status	Planned intention to treat	Allocation concealment	Adequacy of randomization	Baseline migraine similarity	Selective outcome reporting	Risk of bias
Mathew, 1995[43]	DB	No	Unclear	Yes	D	No	Moderate
Freitag, 2002[44]	DB	Yes	Unclear	Yes	F, S & D	No	Low
Klapper, 1997[45]	DB	Yes	Unclear	Yes	D	No	Low
Hering, 1992[46]	DB	No	Unclear	NR	NR	No	Moderate
Jensen, 1994[47]	TB	No	Unclear	Yes	F, S & D	No	Moderate

DB – double-blind
TB – triple - blind
D – duration
F – frequency
S – severity

Appendix Table D32. Strength of evidence of migraine prevention in adults with divalproex vs. placebo, results from randomized controlled clinical trials

Outcome	Daily dose	Reference	Sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
≥ 50% reduction in migraine headache rate	Mean average dose 871 mg/d	Freitag, 2002[44]	239	Low				
≥ 50% reduction in migraine headache rate	Mean average dose 1087 mg/d	Mathew, 1995[43]	107	Moderate				
≥ 50% reduction in migraine headache rate		Pooled	346	Moderate	Yes	No	No	Low
50% improvement in migraine attacks impairing usual activities	500 mg	Klapper, 1997[45]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks impairing usual activities	1000 mg	Klapper, 1997[45]	58	Low	Yes	NA	No	Low
50% improvement in migraine attacks impairing usual activities	1500 mg	Klapper, 1997[45]	59	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	500 mg	Klapper, 1997[45]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg	Klapper, 1997[45]	57	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg	Klapper, 1997[45]	59	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomitingvomiting, phonophobia or photophobia	500 mg	Klapper, 1997[45]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomitingvomiting, phonophobia or photophobia	1000 mg	Klapper, 1997[45]	58	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomitingvomiting, phonophobia or photophobia	1500 mg	Klapper, 1997[45]	59	Low	Yes	NA	No	Low

NA –not applicable

Appendix Table D33. Migraine prevention in adults with divalproex vs. placebo, results from randomized controlled clinical trials

Outcome	Daily dose	Reference Risk of bias	Events/randomized with divalproex	Events/randomized with placebo	Rate,% with divalproex [placebo]	Relative risk (95%CI)	Absolute risk difference (95%CI)
≥ 50% reduction in migraine headache rate	**Mean average dose 871 mg/d**	**Freitag, 2002[44] Risk of bias Low**	**50/123**	**32/116**	**40.7 [27.6]**	**1.5 (1.0 to 2.1)**	**0.13 (0.01 to 0.25)**
≥ 50% reduction in migraine headache rate	**Mean average dose 1087 mg/d**	**Mathew, 1995[43] Risk of bias Moderate**	**33/70**	**5/37**	**47.1 [13.5]**	**3.5 (1.5 to 8.2)**	**0.34 (0.18 to 0.50)**
≥ 50% reduction in migraine headache rate		Pooled	83/193	37/153	43.0 [24.2]	2.1 (0.9 to 4.7)	**0.23 (0.03 to 0.43)**
≥ 50% reduction in migraine headache rate		Heterogeneity				p = 0.068/0.699	p = 0.044/0.754
50% improvement in migraine attacks impairing usual activities	500 mg	Klapper, 1997[45] Risk of bias Low	26/45	4/15	57.8 [25.0]	2.2 (0.9 to 5.2)	0.31 (0.04 to 0.58)
50% improvement in migraine attacks impairing usual activities	1000 mg	Klapper, 1997[45] Risk of bias Low	16/43	4/14	37.2 [25.0]	1.4 (0.6 to 3.5)	0.11 (-0.16 to 0.37)
50% improvement in migraine attacks impairing usual activities	1500 mg	Klapper, 1997[45] Risk of bias Low	24/44	4/15	54.5 [25.0]	2.0 (0.8 to 4.9)	**0.28 (0.01 to 0.55)**
50% improvement in migraine attacks necessitating symptomatic medication	500 mg	Klapper, 1997[45] Risk of bias Low	19/45	2/15	42.2 [13.6]	3.2 (0.8 to 12.0)	**0.29 (0.06 to 0.51)**
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg	Klapper, 1997[45] Risk of bias Low	16/43	2/14	37.2 [13.6]	2.6 (0.7 to 10.0)	0.23 (0.00 to 0.46)
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg	Klapper, 1997[45] Risk of bias Low	19/44	2/15	43.2 [13.6]	3.2 (0.9 to 12.3)	**0.30 (0.07 to 0.52)**

Appendix Table 33. Migraine prevention in adults with divalproex vs. placebo, the results from randomized controlled clinical trials (continued)

Outcome	Daily dose	Reference Risk of bias	Events/randomized with divalproex	Events/randomized with placebo	Rate,% with divalproex [placebo]	Relative risk (95%CI)	Absolute risk difference (95%CI)
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	500 mg	Klapper, 1997[45] Risk of bias Low	21/45	3/15	46.7 [18.2]	2.3 (0.8 to 6.7)	**0.27 (0.02 to 0.52)**
50% improvement in migraine attacks with nausea, vomitting, phonophobia or photophobia	1000 mg	Klapper, 1997[45] Risk of bias Low	18/43	3/14	41.9 [18.2]	2.1 (0.7 to 6.1)	0.22 (-0.03 to 0.47)
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	**1500 mg**	Klapper, 1997[45] **Risk of bias Low**	**22/44**	**3/15**	**50.0 [18.2]**	**2.5 (0.9 to 7.2)**	**0.30 (0.05 to 0.55)**

Bold – significant at 95% confidence limit
CI – confidence level

Appendix Table D34. Migraine frequency, severity, and drug utilization with valproate vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trials

Outcome	Daily dose	Reference	Mean [standard deviation] with valproate	Mean [standard deviation] with placebo	Randomized to valproate vs. placebo	Mean difference (95% CI)	Standardized mean difference (95% CI)
Mean number of days with migraine	1000mg to 1500 mg per day	Jensen, 1994[47]	3.5 [4.8]	6.1 [7.7]	43 [43]	-2.6 (-5.3 to 0.1)	-0.4 (-0.8 to 0.0)
Total drug consumption	**1000mg to 1500 mg per day**	Jensen, 1994[47]	**NR [NR]**	**NR [NR]**	**43 [43]**	**p value <0.001**	
Consumption of symptomatic medication per attack	1000mg to 1500 mg per day	Jensen, 1994[47]	NR [NR]	NR [NR]	43 [43]	p value 0.61	
Mean number of attacks (4 weeks)	**400 mg twice a day**	Hering, 1992[46]	**8.8 [6.1]**	**15.6 [8.3]**	**32 [32]**	**-6.8 (-10.3 to -3.2)**	**-0.9 (-1.4 to -0.4)**
Duration of the remaining attack (hours)	1000mg to 1500 mg per day	Jensen, 1994[47]	11.1 [NR]	11.5 [NR]	43 [43]	p value 0.9	
Duration of the attack (hours)	**400 mg twice a day**	Hering, 1992[46]	**1731.0 [NR]**	**2789.0 [NR]**	**32 [32]**	**p value0.002**	
Intensity of the remaining attacks (no details provided)	1000mg to 1500 mg per day	Jensen, 1994[47]	2.3 [NR]	2.3 [NR]	43 [43]	p value0.45	
Mean number of severe migraine attacks (4 weeks)	**400 mg twice a day**	Hering, 1992[46]	**14.6 [9.8]**	**24.0 [15.4]**	**32 [32]**	**-9.4 (-15.7 to -3.1)**	**-0.7 (-1.2 to -0.2)**

Bold - significant at 95% confidence limit
CI - confidence level
NR - not reported

Appendix Table D35. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
Diamond, 1976[48] Sample 83 80.7% women	To evaluate propranolol in the prophylaxis of migraine	Classic or common migraine (Ad Hoc Committee)	Not reported	Mean: 38.1	Not reported
Stensrud, 1976[49] Stensrud, 1976[49] Sample 20 70% women	To investigate the effects of propranolol in the racemic form (Inderal) and d-propranolol.	Common and classic migraine (as defined by the Ad Hoc Committee)	Not reported	43.5	Not reported
Forssman, 1976[50] Sample 40 87.5% women	To compare the preventive effect of propranolol on migraine attacks with placebo in a double-blind crossover trial	Not reported	18.9	Mean: 37.4	Not reported
Pradalier, 1989[51] Sample 55 76% women	To evaluate the efficacy and tolerability of long-acting propranolol in migraine	International Headache Society	Not reported	Mean: 37.4	Mean frequency of migraine (month): 4
Nadelman, 1986[52] Sample 57 85.5% women	To compare the relative efficacy and safety of propranolol with that of placebo in the prophylaxis of migraine headache	Classic and/or common migraine headaches as set forth by the Ad Hoc Committee on the Classification of Headache	1-5: 22.6%; 6-10: 27.4%; 11-15: 14.5%; 16-20: 9.7%; 21-25: 8.1%; 26+: 17.7%	Not reported	Headache Unit Index: 1.09
Sargent, 1985[53] Sample 149 79% women	To evaluate the prophylactic effect and tolerance of naproxen sodium compared to propranolol hydrochloride and placebo in migraine	Common or classical migraine, or a combination migraine and muscle contraction headache (no definition provided)	20	Mean: 30	Not reported
Ahuja, 1985[54] Sample 26 46.2% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
Malvea, 1973[55] Sample 31 87% women	To determine the relative effectiveness of propranolol in the prevention of migraine as compared to a placebo in a double-blind trial	Not reported	Not reported	Not reported (ranges: 25-57)	Average headache units: 25.4 (no definition provided)
Wideroe, 1974[56] Sample 30	To investigate the value of propranolol in preventing	Classic or common migraine (Ad Hoc Committee, 1962)	Not reported	Mean: 40	All except four patients had two or

Appendix Table 35. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
86.7% women	attacks of migraine				more attacks a month
Palferman, 1983[57] Sample 36 80% women	To assess the efficacy of prophylactic propranolol on the severity and frequency of their symptoms	Episodic headache with other accepted disorders of cerebral function including visual disturbances and vomiting	17.5 (all patients: 11.3)	Mean: 41.4 (all patients: 37.8)	Not reported
Tfelt-Hansen, 1984[58] Sample 96 74% women	To compare the beta-adrenergic blocker timolol to an established drug, propranolol, and to placebo for prophylactic effect in common migraine	Between 2 and 6 common migraine attacks per month as defined by the ad hoc committee and by Olsen	20.9	Mean: 39.5	Number of migraine attacks per 4 weeks: 5.7
Standnes, 1982[59] Sample 25 80% women	To evaluate the prophylactic effect of timolol in migraine	Common migraine attacks (as defined by the Ad Hoc Committee)	Not reported	Mean: 41.4	Mean number of attacks (4 weeks): 6.65
Stensrud, 1980[60] Sample 35 68.6% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
al-Qassab, 1993[61] Sample 45 80% women	To assess the effectiveness of two different doses of a long-acting formulation of propranolol (propranolol LA) in patients with severe migraine	Diagnosis of migraine was made on clinical assessment.	Median: 9	Median: 36	Median attacks (month): 4
Diener, 2004[42] Sample 575 79.8% women	To evaluate the efficacy and safety of two doses of topiramate and safety of two doses of topiramate vs. placebo for migraine prophylaxis, with propranolol (PROP) as an active control	International Headache Society	Not reported	Median: 41	Mean monthly migraine frequency: 5.1
Rafieian-Kopaei, 2005[62] Sample 105 % women Not reported	To compare the prophylactic activity of propranolol and amitriptyline on frequency,	Migraine (International Headache Society)	>1 (from inclusion criteria)	Not reported	Mean attack frequency: 4.02 (per month)

Appendix Table 35. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
	duration and severity of migraine attacks				
Weber, 1972[63] Sample 25 52% women	To compare the prophylactic effect of the propranolol to placebo	Migraine (Classification of headache, JAMA (1962) 179, 717)	Not reported	Mean: 40.6	Not reported
Pradalier, 1989[64] Sample 55 75.7% women	To assess the efficacy and safety of long-acting propranolol (LA. P) 160 mg once-daily in the prpphylactic treatment of migraine	Migraine (International Headache Society)	Not reported	Not reported	Not reported
Kuritzky, 1987[65] Sample 38 % women Not reported	1) To evaluate the efficacy of long acting propranolol (Deralin SR) in reducing the frequency, duration and severity of migraine when compared with placebo, 2) To register possible side effects, and 3) to study correlation between plasma propranolol levels and clinical effectiveness in migraine.	Not reported (While eligibility criteria are not reported, author described "classic or common migraine" patients were included.)	14.2	Not reported	Mean number of migraine attacks: 3 (""All patients averaged at least 3 attacks per month when untreated.")

Appendix Table D36. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed - relationships
Diamond, 1976[48]	Not reported	Not reported	Yes	Not reported	Not reported
Stensrud, 1976[49]	Not reported	Not reported	Not reported	Not reported	Not reported
Forssman, 1976[50]	Not reported	Not reported	Not reported	Not reported	Not reported
Pradalier, 1989[51]	Not reported	Not reported	Yes	Not reported	Not reported
Nadelmann, 1986[52]	Not reported	Not reported	Yes	Unclear	Two authors are employed by pharmaceutical industry (Ayerst Laboratories), but unclear their relationship (no funding source reported.)
Sargent, 1985[53]	Not reported	Not reported	Not reported	Not reported	Not reported
Ahuja, 1985[54]	Industry (Inderal brand of propranolol and identical looking placebo tablets were supplied by Alkali and Chemical Corp. India Ltd.	Not reported	Not reported	Not reported	Not reported
Malvea, 1973[55]	Industry	Not reported	Not reported	Not reported	Not reported
Wideroe, 1974[56]	Not reported	Not reported	Not reported	Not reported	Not reported
Palferman, 1983[57]	Industry (all tablets were supplied by ICI Pharaceuticals.)	Not reported	Not reported	Not reported	Not reported
Tfelt-Hansen, 1984[58]	Not reported	Not reported	Yes	Not reported	Not reported
Standnes, 1982[59]	Industry	Not reported	Yes	Not reported	Not reported
Stensrud, 1980[60]	Not reported	Not reported	Not reported	Not reported	Not reported
al-Qassab, 1993[61]	Industry	Yes	Yes	Not reported	Not reported
Diener, 2004[42]	Industry	Yes	Yes	Yes	Hans-Christoph Diener has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from 3M Medica, Allergan, Almirall Prodesfarma, AstraZeneca, Bayer Vital, Böhringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, La Roche, Lilly, Novartis, MSD,Parke-Davis,Pfizer,Pharmacia,Pierre Fabre,Schaper and Brümmer, and Weber & Weber. Peer Tfelt-Hansen has been a consultant/scientific advisor for, and/or has received honoraria for oral presentation from Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, MSD, Pfizer, and Quintiles. Carl Dahlöf has been a

Appendix Table 36. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed - relationships
					consultant/scientific advisor for, and has received honoraria for oral presentations from Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Jansen-Cilag, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Pharmacia, and Pierre Fabre. Miguel JA Láinez has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Almirall Prodesfarma,AstraZeneca, Böhringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, MSD, Novartis, Pfizer, Pierre Fabre, and Sanofi-Synthelabo. Giorgio Sandrini has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Allergan, AstraZeneca, Bayer, Bristol- Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, Lilly,MSD, Pfizer, Pharmacia, and Solvay Pharma. Shuu-Jiun Wang has received grant/research support from and/or received honoraria for oral presentations from AstraZeneca, Glaxo-SmithKline, Johnson & Johnson, Lilly,MSD, and Pfizer. Walter Neto, Ujjwalla Vijapurkar, Aiden Doyle, and David Jacobs are employed by Johnson & Johnson Pharmaceutical Research and Development, LLC.
Rafieian-Kopaei, 2005[62]	Other	Not reported	Yes	Not reported	All authors are from the University that sponsored the study
Weber, 1972[63]	Industry (Drugs were provided by Ayerst laboratories)	Not reported	Not reported	Unclear	Dr. Trent and Kyle of Ayerst laboratories assisted in the study. Their contribution not known.
Pradalier, 1989[64]	Not reported	Not reported	Not reported	Not reported	Not reported
Kuritzky, 1987[65]	Not reported	Yes	Yes	Not reported	Not reported

Appendix Table D37. Risk of bias in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference	Masking treatment status	Planned intention to treat	Allocation concealment	Adequacy of randomization	Baseline similarity by migraine status	Selective outcome reporting	Risk of bias
Diamond, 1976[48]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Stensrud, 1976[49]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Forssman, 1976[50]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Pradalier, 1989[51]	Double blind	Yes	Unclear	Yes	F & S	Unclear	Low
Nadelmann, 1986[52]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Sargent, 1985[53]	Double blind	No	Unclear	Yes	Not reported	Unclear	Moderate
Ahuja, 1985[54]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Low
Malvea, 1973[55]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Wideroe, 1974[56]	Double blind	No	Unclear	Not reported	S	Unclear	Moderate
Palferman, 1983[57]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Tfelt-Hansen, 1984[58]	Double blind	No	Unclear	Yes	F, S & D	Unclear	Moderate
Standnes, 1982[59]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Stensrud, 1980[60]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
al-Qassab, 1993[61]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Diener, 2004[42]	Double blind	Yes	Unclear	Yes	F	Unclear	Low
Rafieian-Kopaei, 2005[62]	Double blind	No	Unclear	Not reported	F	Unclear	Moderate
Weber, 1972[63]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Pradalier, 1989[64]	Double blind	Yes	Unclear	Not reported	Not reported	Unclear	Low
Kuritzky, 1987[65]	Open-label	No	Unclear	Not reported	Not reported	Unclear	High

F - monthly migraine frequency; S - migraine severity; D - migraine duration

Appendix Table D38. Strength of evidence of migraine prevention with propranolol (randomized controlled clinical trials)

Reference	Active drug	Control drug	Sample size	Ris of bias	Directness	Consistency	Precision	Strength of evidence
Tfelt-Hansen, 1984[58]				Moderate				
Diener, 2004[42]				Low				
Standnes, 1982[59]				Moderate				
Diamond, 1976[48]				Moderate				
Weber, 1972[63]				Moderate				
Pooled	Propranolol	Placebo	559	Moderate	Yes	Consistency	No	Low
Diener, 2004[42]	Topiramate	Propranolol	288	Low	Yes	Not applicable	No	Low
Kaniecki, 1997[66]	Divalproex	Propranolol	74	High	Yes	Not applicable	No	Insufficient
Kass, 1980[67]	Propranolol	Clonidine	46	Moderate	Yes	Not applicable	No	Low
Olerud, 1986,[68]	Propranolol	Cinnarizine	28	Low	Yes	Not applicable	No	Low
Kangasniemi, 1984[69]				Moderate				
Gerber, 1991[70]				Moderate				
Pooled	Propranolol	Metoprolol.	113	Moderate	Yes	Yes	No	Low
Sudilovsky, 1987[71]	Propranolol	Nadolol	93	Moderate	Yes	Not applicable	No	Low
Olerud, 1986[68]	Nadolol	Propranolol	28	Moderate	Yes	Not applicable	No	Low
Tfelt-Hansen, 1984[58]				Moderate				
Standnes, 1982[59]				Moderate				
Pooled	Timolol	Propranolol	242	Moderate	Yes	Yes	No	Low
Gerber, 1991[70]	Propranolol	Nifedipine	36	Moderate				Low
Albers, 1989[72]	Propranolol	Nifedipine	40	High				Low
Pooled	Propranolol	Nifedipine	76	High	Yes	Yes	No	Low
Domingues, 2009[73]	Propranolol	Nortriptyline	49	Moderate	Yes	Not applicable	No	Low
Ziegler, 1987[74]	Propranolol	Amitriptyline	108	Moderate	Yes	Not applicable	Yes	Low
Kangasniemi, 1983[75]	Propranolol	Femoxetine	29	Moderate	Yes	Not applicable	No	Low
Olerud, 1986[68]	Propranolol	Propranolol + Cinnarizine	28	Low	Yes	Not applicable	No	Low
Domingues, 2009[73]	Nortriptyline	Propranolol + Nortriptyline	51	Moderate	Yes	Not applicable	No	Low
Domingues, 2009[73]	Propranolol	Propranolol + Nortriptyline	52	Moderate	Yes	Not applicable	No	Low

Appendix Table D39. Migraine prevention with propranolol, results from randomized controlled clinical trials

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
Number of responder (patients with 50% reduction in frequency)	**Tfelt-Hansen, 1984[58] Risk of bias Moderate**	**Propranolol 80 mg b.i.d. (plus timolol placebo)**	**Placebo**	**48/96**	**12/48**	**50.0 [25.0]**	**2.0 (1.2 to 3.4)**	**0.25 (0.09 to 0.41)**
≥ 50% reduction of average monthly migraine frequency	**Diener, 2004[42] Risk of bias Low**	**Propranolol 160 mg/d**	**Placebo**	**62/144**	**11/49**	**43.1 [21.9]**	**1.9 (1.1 to 3.3)**	**0.21 (0.06 to 0.35)**
≥ 50% reduction of frequency of attack	Standnes, 1982[59] Risk of bias Moderate	Propranolol 80 mg + (timolol placebo)	Placebo timolol placebo + Propranolol placebo	13/25	3/13	52.0 [24.0]	2.3 (0.8 to 6.5)	0.29 (-0.01 to 0.59)
Responder (defined as patient preference)	**Diamond, 1976[48] Risk of bias Moderate**	**Propranolol 80 or 160 mg**	**Placebo**	**34/83**	**17/83**	**41.0 [20.5]**	**2.0 (1.2 to 3.3)**	**0.21 (0.07 to 0.34)**
Symptomatic response: Good or Excellent; All or nearly all symptoms of migraine absent PLUS more than 50% reduction in frequency or severity of headache	Weber, 1972[63] Risk of bias Moderate	Propranolol 80 mg (20mg x 4 times daily)	Placebo	5/8	0/11	62.5 [0.0]	14.7 (0.9 to 232.4)	**0.63 (0.29 to 0.96)**
Clinical response at least 50%	**Pooled with random effects model**	**Propranolol**	**Placebo**	**162/356**	**43/204**	**45.5 [21.0]**	**2.0 (1.5 to 2.7)**	**0.26 (0.16 to 0.35)**

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
reduction in migraine frequency								
	Heterogeneity						0.0 (p=0.726 to I-squared (variation in RR Attributable Due heterogeneity)=0.0%)	0.00 (p=0.234 to I-squared (variation in RD Attributable Due heterogeneity)=28.1%)
≥50% reduction of average monthly migraine frequency	Diener, 2004[42] Risk of bias Low	Topiramate 100 mg/d	Propranolol 160 mg/d	52/0	62/0	36.9 [43.1]	0.9 (0.6 to 1.1)	-0.06 (-0.18 to 0.05)
≥ 50% reduction of average monthly migraine frequency	Diener, 2004[42] Risk of bias Low	Topiramate 200 mg/d	Propranolol 160 mg/d	50/0	62/0	34.7 [43.1]	0.8 (0.6 to 1.1)	-0.08 (-0.20 to 0.03)
Patients responding with a 50% or greater reduction in mean migraine frequency (month)	Kaniecki, 1997[66] Risk of bias High	Divalproex Mean dose: 1414mg/d	Propranolol Mean dose: 174mg/d	21/0	20/0	56.8 [54.1]	1.1 (0.7 to 1.6)	0.03 (-0.20 to 0.25)
Patients responding with a 50% or greater reduction in mean migraine days (month)	Kaniecki, 1997[66] Risk of bias High	Divalproex Mean dose: 1414mg/d	Propranolol Mean dose: 174mg/d	21/0	22/0	56.8 [59.5]	1.0 (0.6 to 1.4)	-0.03 (-0.25 to 0.20)
>50% reduction of	Kass, 1980[67] Risk of bias	Propranolol 160 mg (two 40	Clonidine 100 µg (two	13/23	8/23	56.5 [34.8]	1.6 (0.8 to 3.2)	0.22 (-0.06 to 0.50)

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95%CI)	Absolute risk difference (95%CI)
headache days, 4 weeks (comparing pretreatment period with the last 4 wks of treatment)	Moderate	mg tablets twice daily)	25 µg tablets twice daily)					
50% reduction of migraine attacks	Olerud, 1986 [68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Cinnarizine (+ placebo) 25-75 mg	1/14	2/14	7.1 [14.3]	0.5 (0.1 to 4.9)	-0.07 (-0.30 to 0.16)
75% reduction of migraine attacks	Olerud, 1986 [68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Cinnarizine (+ placebo) 25-75 mg	5/14	2/14	35.7 [14.3]	2.5 (0.6 to 10.8)	0.21 (-0.10 to 0.53)
100% reduction of migraine attacks	Olerud, 1986 [68] **Risk of bias Low**	**Propranolol LA (+ placebo) 80-120 mg**	**Cinnarizine (+ placebo) 25-75 mg**	**7/14**	**1/14**	**50.0 [7.1]**	**7.0 (1.0 to 49.7)**	**0.43 (0.13 to 0.72)**
75% reduction of migraine attacks	Olerud, 1986 [68] **Risk of bias Low**	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	Cinnarizine (+ placebo) 25-75 mg	2/14	2/14	14.3 [14.3]	1.0 (0.2 to 6.1)	0.00 (-0.26 to 0.26)
100% reduction of migraine attacks	Olerud, 1986 [68] **Risk of bias Low**	**Propranolol: 80 mg/d+ Cinnarizine 25-75 mg/d**	**Cinnarizine (+ placebo) 25-75 mg**	**12/14**	**1/14**	**85.7 [7.1]**	**12.0 (1.8 to 80.3)**	**0.79 (0.56 to 1.01)**
50% reduction of migraine attacks	Olerud, 1986 [68] **Risk of bias Low**	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	Cinnarizine (+ placebo) 25-75 mg	0/14	2/14	0.0 [14.3]	0.2 (0.0 to 3.8)	-0.14 (-0.35 to 0.07)
≥50% reduction of	Kangasniemi, 1984[69]	Propranolol 80 mg b.i.d.	Metoprolol 200 mg o.m.	15/36	17/36	41. 7 [47.2]	0.9 (0.5 to 1.5)	-0.06 (-0.29 to 0.17)

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
the sum of severity scores	Risk of bias Moderate							
Responder of Migraine days	Gerber, 1991[70] Risk of bias Moderate	Propranolol Hydrochloride 160 m/day (HD)	Metoprolol 200 mg / day (HD)	6/19	12/22	31.6 [54.5]	0.6 (0.3 to 1.2)	-0.23 (-0.53 to 0.07)
	Pooled with random effects model	Propranolol	Metoprolol	21/55	29/58	38.2 [50.0]	0.8 (0.5 to 1.2)	-0.12 (-0.30 to 0.06)
	Heterogeneity						p=0.371 (I-squared (variation in RR Attributable Due heterogeneity)=0.0% to 0.0)	p=0.361 (I-squared (variation in RD Attributable Due heterogeneity)=0.0% to 0.00)
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	4/44	13/49	9.1 [26.5]	0.3 (0.1 to 1.0)	-0.17 (-0.32 to -0.02)
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[71] **Risk of bias Moderate**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**4/44**	**17/47**	**9.1 [36.2]**	**0.3 (0.1 to 0.7)**	**-0.27 (-0.43 to -0.11)**
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	5/44	11/49	11.4 [22.4]	0.5 (0.2 to 1.3)	-0.11 (-0.26 to 0.04)
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[71] **Risk of bias Moderate**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**5/44**	**18/47**	**11.4 [38.3]**	**0.3 (0.1 to 0.7)**	**-0.27 (-0.44 to -0.10)**
≥50% reduction of headache intensity	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	8/44	14/49	18.2 [28.6]	0.6 (0.3 to 1.4)	-0.10 (-0.27 to 0.07)

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
≥50% reduction of headache intensity	Sudilovsky, 1987[71] **Risk of bias Moderate**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**8/44**	**19/47**	**18.2 [40.4]**	**0.4 (0.2 to 0.9)**	**-0.22 (-0.40 to -0.04)**
≥50% reduction of headache intensity	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	10/44	11/49	22.7 [22.4]	1.0 (0.5 to 2.2)	0.00 (-0.17 to 0.17)
≥50% reduction of headache intensity	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 160 mg o.d.	10/44	21/47	22.7 [44.7]	0.5 (0.3 to 1.0)	**-0.22 (-0.41 to -0.03)**
≥50% reduction of pain days	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	8/44	9/49	18.2 [18.4]	1.0 (0.4 to 2.3)	0.00 (-0.16 to 0.16)
≥50% reduction of pain days	Sudilovsky, 1987[71] **Risk of bias Moderate**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**8/44**	**19/47**	**18.2 [40.4]**	**0.4 (0.2 to 0.9)**	**-0.22 (-0.40 to -0.04)**
≥50% reduction of pain days	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	9/44	11/49	20.5 [22.4]	0.9 (0.4 to 2.0)	-0.02 (-0.19 to 0.15)
≥50% reduction of pain days	Sudilovsky, 1987[71] Risk of bias Moderate	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 160 mg o.d.	9/44	18/47	20.5[38.3]	0.5 (0.3 to 1.1)	-0.18 (-0.36 to 0.00)
>50% reduction of number of migraine attacks compared to placebo period	Sudilovsky, 1987[71] Risk of bias Moderate	Nadolol 80 mg/daily (every morning + matching placebo tablet every night)	Propranolol 80 mg (40 mg twice daily)	5/13	9/15	38.5 [60.0]	0.6 (0.3 to 1.4)	-0.22 (-0.58 to 0.15)
Number of responder (patients with 50% reduction in frequency)	Tfelt-Hansen, 1984[58] Risk of bias Moderate	Timolol 10 mg b.i.d. (plus propranolol placebo)	Propranolol 80 mg b.i.d. (plus timolol placebo)	44/96	48/96	45.8 [50.0]	0.9 (0.7 to 1.2)	-0.04 (-0.18 to 0.10)

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
≥50% reduction of frequency of attack	Standnes, 1982[59] Risk of bias Moderate	Timolol 10 mg + (propranolol placebo)	Propranolol 80 mg + (timolol placebo)	14/25	13/25	56.0 [52.0]	1.1 (0.6 to 1.8)	0.04 (-0.24 to 0.32)
	Pooled with random effects	Timolol	Propranolol	58/121	61/121	47.9 [50.4]	1.0 (0.7 to 1.2)	-0.03 (-0.15 to 0.10)
	Heterogeneity						p=0.593 (I-squared (variation in RR Attributable Due heterogeneity)=0.0% to 0.0)	p=0.606 (I-squared (variation in RD Attributable Due heterogeneity)=0.0% to 0.00)
Responder of Migraine days	Gerber, 1991[70] Risk of bias Moderate	Propranolol Hydrochloride 80 mg / day	Nifedipine 20 mg/day	0/19	0/17	0.0 [0.0]	0.0 (0.0 to 0.0)	0.00 (-0.10 to 0.10)
Responder of Migraine days	Gerber, 1991[70] Risk of bias Moderate	Propranolol Hydrochloride 40 mg / day (R3)	Nifedipine 10 mg/day (R3)	3/19	0/17	15.8 [0.0]	6.3 (0.3 to 113.8)	0.16 (-0.03 to 0.34)
Responder of Migraine days	Gerber, 1991[70] Risk of bias Moderate	Propranolol Hydrochloride 120 mg / day (R1)	Nifedipine 30 mg/day (R1)	4/19	2/17	21.1 [11.8]	1.8 (0.4 to 8.6)	0.09 (-0.15 to 0.33)
Responder of Migraine days	Gerber, 1991[70] Risk of bias Moderate	Propranolol Hydrochloride 160 mg / day (HD)	Nifedipine 40 mg/day (HD)	6/19	1/17	31.6 [5.9]	5.4 (0.7 to 40.2)	0.26 (0.02 to 0.49)
Drug efficacy: >50% improvement	Albers, 1989[72] Risk of bias High	Propranolol 60 mg TID	Nifedipine 30 mg TID	12/20	6/20	60.0 [30.0]	2.0 (0.9 to 4.3)	0.30 (0.01 to 0.59)
Reduction by 50% or more in migraine days	**Pooled with random effects models**	**Propranolol 160-180mg**	**Nifedipine**	18/39	7/37	46.2 [18.9]	**2.3 (1.1 to 4.6)**	**0.27 (0.09 to 0.46)**
	Heterogeneity						p=0.368 (I-squared (variation in RR Attributable Due heterogeneity)=0.0% to 0.0)	p=0.823 (I-squared (variation in RD Attributable Due heterogeneity)=0.0% to 0.00)

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
≥50% reduction of the number of days with headache	Domingues, 2009[73] Risk of bias Moderate	Propranolol 40 mg/d	Nortriptyline 20 mg/d	11/25	7/24	33.3 [39.3]	1.5 (0.7 to 3.2)	0.15 (-0.12 to 0.41)
Good response: fall in headache score (compared with placebo treatment) of 50% or more	Ziegler, 1987[74] Risk of bias Moderate	Propranolol 80-240 mg/d	Amitriptyline 50-150 mg/d	12/54	10/54	19.2 [21.4]	1.2 (0.6 to 2.5)	0.04 (-0.11 to 0.19)
>50% reduction of frequency of attack	Kangasniemi, 1983[75] Risk of bias Moderate	Propranolol 80 mg twice a day	Femoxetine 200 mg twice a day	3/15	1/14	20.0 [7.1]	2.8 (0.3 to 23.9)	0.13 (-0.11 to 0.37)
50% reduction of migraine attacks	Olerud, 1986,[68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	1/14	0/14	7.1 [0.0]	3.0 (0.1 to 67.9)	0.07 (-0.11 to 0.25)
75% reduction of migraine attacks	Olerud, 1986[68] Nadolol and propranolol in migraine management. Headache, 10 Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	5/14	2/14	35. 7[14.3]	2.5 (0.6 to 10.8)	0.21 (-0.10 to 0.53)
100% reduction of migraine attacks	Olerud, 1986[68] **Risk of bias Low**	**Propranolol LA (+placebo) 80-120 mg**	**Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d**	**7/14**	**12/14**	**50.0 [85.7]**	**0.6 (0.3 to 1.0)**	**-0.36 (-0.68 to -0.04)**

Appendix Table 39. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition outcomes	Reference Risk of bias	Active drug, daily dose	Control, daily dose	Events/ randomized with active drug	Events/ randomized with control	Rate,% with active [control] treatments	Relative risk (95% CI)	Absolute risk difference (95% CI)
≥50% reduction of the number of days with headache	Domingues, 2009[73] Risk of bias Moderate	Nortriptyline 20 mg/d	Propranolol + Nortriptyline	7/24	10/27	29.2 [37.0]	0.8 (0.4 to 1.7)	-0.08 (-0.34 to 0.18)
50% reduction of migraine attacks	Olerud, 1986)[68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	1/14	0/14	7.1 [0.0]	3.0 (0.1 to 67.9)	0.07 (-0.11 to 0.25)
75% reduction of migraine attacks	Olerud, 1986[68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	5/14	2/14	35.7 [14.3]	2.5 (0.6 to 10.8)	0.21 (-0.10 to 0.53)
100% reduction of migraine attacks	Olerud, 1986[68] Risk of bias Low	Propranolol LA (+ placebo) 80-120 mg	Propranolol + Cinnarizine Propranolol: 80 mg/d; Cinnarizine 25-75 mg/d	7/14	12/14	50.0 [85.7]	0.6 (0.3 to 1.0)	-0.36 (-0.68 to -0.04)
≥ 50% reduction of the number of days with headache	Domingues, 2009[73] Risk of bias Moderate	Propranolol 40 mg/d	Propranolol + Nortriptyline	11/25	10/27	44.0 [37.0]	1.2 (0.6 to 2.3)	0.07 (-0.20 to 0.34)

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D40. Strength of evidence of migraine prevention with timolol

Sample size, references	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Tfelt-Hansen, 1984[58] Standnes, 1982[59] Stellar, 1984[76] 276[58, 59, 76]	Moderate	Yes	Yes	Yes	Moderate

Appendix Table D41. Reduction in frequency of migraine attack by at least 50% from baseline with timolol 10mg twice a day (pooled with random effects model results from randomized controlled clinical trials)

Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with placebo	Rate,% with active drug [placebo]	Relative risk (95% CI)	Weight, random effects Inverse variance	Absolute risk difference (95% CI)	Weight, Random effects inverse variance
Tfelt-Hansen, 1984[58] Moderate	44/96	12/48	45.8[25.0]	1.8 (1.1 to 3.1)	49.32	0.21 (0.05 to 0.37)	49.78
Standnes, 1982[59] Moderate	14/25	3/13	56.0[24.0]	2.4 (0.8 to 6.9)	12.82	0.33 (0.03 to 0.63)	13.75
Stellar, 1984[76] Moderate	25/47	10/47	53.2[21.3]	2.5 (1.4 to 4.6)	37.86	0.32 (0.14 to 0.50)	36.47
Pooled	83/168	25/108	49.4[23.3]	2.1 (1.5 to 3.1)	100	0.27 (0.15 to 0.38)	100
Heterogeneity test				p = 0.732	I-squared=0.0%	p = 0.606	I-squared = 0.0%

CI – confidence interval

Appendix Table D42. Reduction in migraine attack frequency and severity with timolol 10mg twice a day (results from randomized controlled clinical trial[58])

Outcomes	Mean [Standard deviation] with drug	Mean [Standard deviation] with placebo	Mean difference (95% CI)	Standardized Mean difference (95% CI)	Mean ratio (95% CI)
Frequency of attacks	**3.4 [3.1]**	**4.8 [3.9]**	**-1.5 (-2.5 to -0.5)**	**-0.4 (-0.7 to -0.1)**	**0.7 (0.5 to 1.0)**
Number of attacks (4 weeks)	**2.8 [NR]**	**4.7 [NR]**	**P<0.01**		
Duration of attacks (hours)	7.4 [7.3]	8.0 [6.7]	-0.5 (-2.5 to 1.4)	-0.1 (-0.4 to 0.2)	0.9 (0.7 to 1.3)
Frequency of attacks with any therapy	**2.8 [3.0]**	**4.2 [3.7]**	**-1.4 (-2.4 to -0.4)**	**-0.4 (-0.7 to -0.1)**	**0.7 (0.5 to 0.9)**
Frequency of attacks with nausea	1.4 [1.9]	1.9 [2.1]	-0.5 (-1.0 to 0.1)	-0.2 (-0.5 to 0.0)	0.7 (0.6 to 0.9)
Headache index (2) (frequency x average severity)	**41.7 [50.2]**	**69.3 [69.4]**	**-27.6 (-44.7 to -10.5)**	**-0.5 (-0.7 to -0.2)**	**0.6 (0.5 to 0.8)**
Headache index (1) (frequency x average severity)	**5.7 [5.1]**	**9.0 [7.3]**	**-3.3 (-5.1 to -1.5)**	**-0.5 (-0.8 to -0.2)**	**0.6 (0.5 to 0.9)**
Severity of attacks	**1. 8 [0.6]**	**1.9 [0.5]**	**-0.2 (-0.3 to 0.0)**	**-0.4 (-0.6 to -0.1)**	**0.9 (0.3 to 2.6)**

Bold - significant at 95% confidence limit
CI - confidence interval

Appendix Table D43. Randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Active drug	Reference Sample Number analyzed % women	Definition of migraine % without aura	Baseline severity	Eligible Age of subjects	Years of migraine % with prior preventative treatment
Acetazolamide	Vahedi, 2002[77] Sample 53 Analyzed 53 % of women 75.5	Migraine (International Headache Society) % without aura 90.6	Attack frequency (4wks): 5	18-65 Mean: 39.2	Years of migraine NR % with prior treatment NR
Gabapentin	Mathew, 2001[78] Sample 145 Analyzed 87 % of women 82.8	Migraine (International Headache Society) % without aura 56.3	Migraine headache frequency during last 6 months: 4.9	16-75 Mean: 39.6	Years of migraine 20.8 % with prior treatment NR
Vigabatrin	Ghose, 2002[79] Sample 23 Analyzed 15 % of women 73.9	Migraine (International Headache Society) % without aura 56.5	Headache frequency (1 wk): 2.14	NR (range: 18-66) Mean: 43.6	Years of migraine NR % with prior treatment Sodium Valproate : 65.2%;
Oxcarbazepine	Silberstein, 2008[80] Sample 170 Analyzed 170 % of women 84.7	Migraine (International Headache Society) % without aura NR	Frequency of migraine headache per month (range, inclusion criteria): 3 to 9	16-65 Mean: 40.5	Years of migraine NR % with prior treatment NR
Gabapentin	Wessely, 1987[81] Sample 45 Analyzed 33 % of women 88.9	Common or classic migraine % without aura NR	Frequency of migraine headache per month: 5.23	NR Mean: 43	Years of migraine NR % with prior treatment NR
Gabapentin	Di Trapani, 2000[82] Sample 63 Analyzed 63 % of women 52.4	Migraine with or without aura according to the international Headache Society Classification of Headache % without aura 50.8	Frequency of migraine attack: 5.24	18-65 NR	Years of migraine NR % with prior treatment NR
Carbamazepinee	Rompel, 1970[83] Sample NR Analyzed 48 % of women 68.8	Typical Migraine (JC: "Authors' definition is available in the manuscript, but it is too long to list here, almost 1 page") % without aura NR	Frequency of migraine attack: 2.97	NR (range: 14-60) NR	Years of migraine NR % with prior treatment NR
Lamotrigine	Steiner, 1997[84] Sample 77 Analyzed 77 % of women 81.8	Migraine (International Headache Society) % without aura 59.7	Frequency of migraine attack: 4.02	18-60 Mean: 37.2	Years of migraine NR (JC: At least 2 years of recognizable attacks was required at entry) % with prior treatment NR

NR – not reported

Appendix Table D44. Funding and conflict of interest in randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Active drug	Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Acetazolamide	Vahedi, 2002[77]	Unclear (Funded from Association pour le Development des Neurosceinces a Lariboisiere)	Yes	Yes	NR	All authors are employed in a hospital.
Gabapentin	Mathew, 2001[78]	NR	Yes	Yes	NR	NR
Vigabatrin	Ghose, 2002[79]	Industry	Yes	Yes	NR	NR
Oxcarbazepine	Silberstein, 2008[80]	Industry	Yes	Yes	Yes	S. Silberstein has received grants for other research or activities not reported in this article and has received honoraria during the course of this study from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year. J. Saper has received honoraria from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year, during the course of this study for other activities not reported in this article. F. Berenson has received honoraria from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year, during the course of this study for other activities not reported in this article. M. Somogyi, K. McCague and J. D'Souza are employees of Novartis Pharmaceuticals Corporation.
Gabapentin	Wessely, 1987[81]	NR	NR	NR	NR	NR
Gabapentin	Di Trapani, 2000[82]	NR	NR	Yes	NR	NR
Carbamazepinee	Rompel, 1970[83]	Industry supplied the drugs.	NR	NR	NR	NR
Lamotrigine	Steiner, 1997[84]	NR	Yes	Yes	NR	NR

NR – not reported

Appendix Table D45. Risk of bias in randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Reference	Masking of treatment status	Planned intention to treat	Allocation concealment	Adequacy of randomization	Baseline migraine similarity	Selective outcome reporting	Risk of bias
Vahedi, 2002[77]	DB	Yes	Yes	Yes	D	Unclear	Low
Mathew, 2001[78]	DB	Yes	Yes	No	F, S & D	Unclear	Moderate
Ghose, 2002[79]	DB	No	Unclear	NR	F	Unclear	Moderate
Silberstein, 2008[80]	DB	Yes	Yes	Yes	F, S & D (D: age at onset provided)	Unclear	Low
Wessely, 1987[81]	DB	No	Unclear	NR	NR	Unclear	Moderate
Di Trapani, 2000[82]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Rompel, 1970[83]	DB	No	Unclear	NR	NR	Unclear	Moderate
Steiner, 1997[84]	DB	Yes	Unclear	NR (No formal testing conducted, and no mention about the random adequacy)	NR (No formal testing conducted, and no mention about the random adequacy)	Unclear	Low

DB – double-blind
F – frequency
D – duration
S – severity
NR – not reported

Appendix Table D46. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference Aim	Total sample [number analyzed] % females in sample	Definition of migraine	Duration of migraine	Presence of aura	Migraine frequency at baseline/month	Age of subjects (mean or median)
Ekbom, 1972[85] To investigate the effect of beta-receptor blocking agents on migraine by using a new compound, LB-46 (d,1-4-indol)	30 [26] 86.7	Ad Hoc Committee, 1962	Not reported	Since 4 had classic migraine it was assumed that these patients had migraine with aura	4	Mean 33.7 years
Sjaastad, 1972[86] To test the efficacy of Visken (LB-46) in migraine prophylaxis with a double-blind technique	28 [24] 85.7	Ad Hoc Committee on classification of headache (1962)	Not reported	Since 14 patients had classical migraine it was assumed that they had migraine with aura	2	Mean 35.8 years
Ekbom, 1975[87] Not reported	33 [28] 81.8	Ad Hoc Committee on classification of headache and World Federation of Neurology's Research Group on Migraine and Headache	Not reported	Since 6 patients had classic migraine it was assumed that these patients had migraine with aura	3	Mean 41.3 years
Nanda, 1978[88] Not reported	43 [33] 74.4	Migraine with the following characteristics: 1) Onset of first attack before age 25 years; 2) No evidence of a progressive neurological deficit over three years; 3) Hemicrania in association with any two of the following:a) family history, b) nausea and vomiting, and c) psychic, visual, or sensory prodroma	Not reported	Not reported	4.8	Not reported
Briggs, 1979[89] To assess the value of timolol in migraine prophylaxis and to elucidate further the reason for the varied response to different beta-blockers.	14 [Variable] 71.4	Ad Hoc Committee on classification of headache	Not reported	Since 2 patients had classical it was assumed that these patients had migraine with aura	2	Not reported
Ryan, 1982[90] Ryan, 1983[91]	80 [80] 77.5	Not reported	Not reported	Not reported	3	Not reported

Appendix Table 46. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total sample [number analyzed] % females in sample	Definition of migraine	Duration of migraine	Presence of aura	Migraine frequency at baseline/month	Age of subjects (mean or median)
To determine the relative efficacy and safety of nadolol in reducing the frequency and/or the severity of migraine attacks as compared to placebo						
Forssman, 1982[92] Forssman, 1983[93] To confirm the use of atenolol in migraine prophylaxis in a double-blind cross-over study with placebo	24 [20] 80.0	Ad Hoc Committee on classification of headache	Not reported	Since the definition of migraine was according to the Ad Hoc Committee classification it was assumed that none of the patients had aura	Not reported	Mean 40 years
Andersson, 1983[94] To evaluate whether metoprolol decreases 1) the frequency, 2) the severity of the migraine attacks, 3) days with migraine, 4) consumptiom of acute migraine medication, compared with placebo in patients with classical and non-classical migraine	71 [65] 84.5	Vahlquist's criteria and World Federation of Neurology Research Group on Migraine and Headache	18.4 years	Not reported	4.8	Mean 39.7 years
Stellar, 1984[76] To compare timolol with placebo	107 [94] 72.0	Ad Hoc Committee on Classification of Headache.	Not reported	Since 5 patients had classic migraine it was assumed that they had migraine with aura.	3	Mean 43 years
Freitag, 1984[95] To evaluate the efficacy of nadolol in reducing the frequency and severity of migraine headaches	32 [32] 81.3	Ad Hoc Committee on classification of headache	Not reported	Since 5 patients had classic migraine it was assumed that they had migraine with aura.	Not reported	Mean 36.3 years
Johannsson, 1987[96] To investigate the prophylactic	72 [63] 69.8	Ad Hoc Committee on classification of headache	26 years	Since the definition of migraine was	2	Mean 43 years

Appendix Table 46. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total sample [number analyzed] % females in sample	Definition of migraine	Duration of migraine	Presence of aura	Migraine frequency at baseline/month	Age of subjects (mean or median)
anti-migraine effect of atenolol, a cardiovascular, water-soluble beta-antagonist				according to the Ad Hoc Committee classification it was assumed that none of the patients had aura		
Kangasneimi, 1987[97] To compare metoprolol with placebo in patients with frequent classic migraine attacks	77 [74] 79.7	NIH Ad Hoc Committee	17.2 years	Since all had classic migraine it was assumed all had migraine with aura	4.3	Mean 37.5 years
van de Ven, 1997[98] To assess the efficacy of bisoprolol in migraine prophylaxis	226 [Not reported] 82.0	Not reported	Age at onset (years): 20.3	23% of patients had migraine with aura and 77% migraine without aura	5.5	Mean 38.7 years
Siniatchkin, 2007[99] To investigate the influence of a controlled-release (CR) form of metoprolol on the amplitude and habituation of the early and late control negative variation (CNV) components using a double-blind, placebo-controlled, parallel-group design with systematic multiple CNV recordings during the treatment phase in order to provide more complete analysis of the treatment process.	20 [20] 85.0	International Headache Society criteria	22.3 years	One of the inclusion criteria was patients having migraine without aura	4.6	Mean 37 years

Appendix Table D47. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference	Funding	Ethical approval	Consensus	Conflict of interest
Ekbom, 1972[85]	Not reported	Not reported	Not reported	Not reported
Sjaastad, 1972[86]	Not reported	Not reported	Not reported	Not reported
Ekbom, 1975[87]	Not reported (however, alprenolol was donated by AB Hassle, Gothenburg, Sweden)	Not reported	Not reported	Not reported
Nanda, 1978[88]	Grant	Not reported	Yes	Not reported
Briggs, 1979[89]	Not reported	Yes	Yes	Not reported
Ryan, 1982[90] Ryan, 1983[91]	Not reported	Not reported	Yes	Not reported
Forssman, 1982[92] Forssman, 1983[93]	Not reported	Not reported	Not reported	Not reported
Andersson, 1983[94]	Not reported	Yes	Yes	Not reported
Stellar, 1984[76]	Not reported	Not reported	Yes	Not reported
Freitag, 1984[95]	Not reported	Not reported	Yes	Not reported
Johannsson, 1987[96]	Not reported	Not reported	Not reported	Not reported
Kangasneimi, 1987[97]	Not reported	Yes	Yes	Not reported
van de Ven, 1997[98]	Industry	Yes	Yes	Not reported
Siniatchkin, 2007[99]	Not reported	Yes	Yes	Not reported

Appendix Table D48. Risk of bias in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Baseline similarity	Selective outcome reporting	Risk of bias
Ekbom, 1972[85]	Double-blind	No	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Moderate
Sjaastad, 1972[86]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Ekbom, 1975[87]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Nanda, 1978[88]	Double-blind	No	Unclear	Not reported	Frequency: similar: Severity: not reported: Duration: not reported	Unclear	Moderate
Briggs, 1979[89]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Ryan, 1982[90] Ryan, 1983[91]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Forssman, 1982[92] Forssman, 1983[93]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Andersson, 1983[94]	Double-blind	No	Unclear	Not reported. However, there were more males in metoprolol group (9/34 as compared to placebo group (2/37); the metoprolol group patients had more years of migraine (22.6 years) as compared to the placebo group (14.6 years)	The metoprolol group patients had more years of migraine (22.6 years) as compared to the placebo group (14.6 years). Frequency and severity of migraine were similar across the groups	Unclear	Moderate
Stellar, 1984[76]	Double-blind	Yes	Unclear	Not adequate (The frequency of headaches with unilateral pain was significantly greater ($p<0.05$) in the timolol-placebo sequency group than in the placebo-timolol group	Frequency: similar; Severity: similar; Duration: similar	Unclear	Moderate

Appendix Table 48. Risk of bias in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Baseline similarity	Selective outcome reporting	Risk of bias
Freitag, 1984[95]	Double-blind	Yes	Unclear	Not reported	Not reported	Unclear	Low
Johannsson, 1987[96]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Kangasneimi, 1987[97]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
van de Ven, 1997[98]	Double-blind	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Moderate
Siniatchkin, 2007[99]	Double-blind	No	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Moderate

Appendix Table D49. Strength of evidence of migraine prevention with beta-blockers in adults (sorted by drug name)

Definition of the outcome	Drug name	Reference	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Better during the period of the trial	Acebutolol	Nanda, 1978[88]	Moderate	Yes	Not applicable	Yes	Low
Better during the period of the trial	Alprenolol	Ekbom, 1975[87]	Moderate	Yes	Not applicable	No	Low
Reduction of integrated headache more than 50%	Atenolol	Forssman, 1982[92] Forssman, 1983[93]	Moderate	Yes	Not applicable	Yes	Low
Reduction of number of attacks more than 50%	Atenolol	Forssman, 1982[92] Forssman, 1983[93]	Moderate	Yes	Not applicable	Yes	Low
Consumption of ergotamine drugs	Atenolol	Forssman, 1982[92] Forssman, 1983[93]	Moderate	Yes	Not applicable	Yes	Low
Patients' subjective judgment of their migraine: complete remission/marked improvement	Metoprolol	Kangasneimi, 1987[97]	Moderate				
		Andersson, 1983[94]	Moderate				
Pooled			Moderate	Yes	Yes	Yes	Moderate
Patients' subjective judgment of their migraine: moderate improvement	Metoprolol	Kangasneimi, 1987[97]	Moderate	Yes	Not applicable	No	Low
Effect: slight	Metoprolol	Andersson, 1983[94]	Moderate	Yes	Not applicable	No	Low
Treatment successful: Frequency	Nadolol	Freitag, 1984[95]	Low	Yes	Not applicable	No	Low
Treatment successful: Intensity	Nadolol	Freitag, 1984[95]	Low	Yes	Not applicable	No	Low
Treatment successful: Pain	Nadolol	Freitag, 1984[95]	Low	Yes	Not applicable	No	Low
Treatment successful: Relief	Nadolol	Freitag, 1984[95]	Low	Yes	Not applicable	No	Low
Completely relieved of migraine	Timolol	Briggs, 1979[89]	Moderate	Yes	Not applicable		Low
Responders (Patients with 50% or greater reduction in headache frequency)	Timolol	Stellar, 1984[76]	Moderate	Yes	Not applicable	No	Low
Week 8:Global response of great or moderate improvement: to only one therapy	Timolol	Stellar, 1984[76]	Moderate	Yes	Not applicable	Yes	Low
Patient rating of medication as extremely or moderately helpful: to only one therapy	Timolol	Stellar, 1984[76]	Moderate	Yes	Not applicable	Yes	Low
Headaches with nausea: frequency per 28 days	Timolol	Stellar, 1984[76]	Moderate	Yes	Not applicable		Low

Appendix Table D50. Efficacy of beta-blockers in prevention of migraine in adults; results from randomized controlled clinical trials (sorted by drug name)

Reference Risk of bias	Drug and dose	Outcome	Events/ Randomized [Rate of outcome with drug, %]	Events/ Randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
Ekbom, 1975[87] Moderate	Alprenolol 200mg/day ("Durules")	Better during the period of the trial	11/33 [33.3%]	12/33 [36.4%]	0.9 (0.5 to 1.8)	-0.03 (-0.26 to 0.2)		
Forssman, 1982[92] Forssman, 1983[93] Moderate	**Atenolol 100mg/day**	**Reduction of integrated headache more than 50%**	**11/24 [45.8%]**	**0/24 [0.0%]**	**23.0 (1.4 to 369.5)**	**0.46 (0.26 to 0.7)**	**2 (2 to 4)**	**458 (255 to 661)**
Forssman, 1982[92] Forssman, 1983[93] Moderate	**Atenolol 100mg/day**	**Reduction of number of attacks more than 50%**	**8/24 [33.3%]**	**0/24 [0.0%]**	**17.0 (1.0 to 278.9)**	**0.33 (0.14 to 0.5)**	**3 (2 to 7)**	**333 (140 to 527)**
Forssman, 1982[92] Forssman, 1983[93] Moderate	**Atenolol 100mg/day**	**Consumption of ergotamine drugs**	**14/24 [58.3%]**	**0/24 [0.0%]**	**29.0 (1.8 to 460.1)**	**0.58 (0.38 to 0.8)**	**2 (1 to 3)**	**583 (382 to 784)**
Kangasneimi, 1987[97] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Patients' evaluation: complete remission/marked improvement**	**29/77 [38.0%]**	**16/77 [21.0%]**	**1.8 (1.1 to 3.1)**	**0.17 (0.03 to 0.3)**	**6 (3 to 36)**	**169 (28 to 310)**
Andersson, 1983[94] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Patients' evaluation: complete remission/marked improvement**	**15/34 [44.1%]**	**6/37 [16.2%]**	**2.7 (1.2 to 6.2)**	**0.28 (0.07 to 0.5)**	**4 (2 to 13)**	**279 (74 to 484)**
		Pooled	**44/111 [39.9%]**	**22/114 [19.4%]**	**2.0 (1.3 to 3.2)**	**0.20 (0.09 to 0.3)**	**5 (3 to 11)**	**204 (88 to 321)**
Kangasneimi, 1987[97] Moderate	Metoprolol 200mg once daily ("Durules")	Patients' subjective judgment of their migraine: moderate improvement	14/77 [18.0%]	15/77 [19.0%]	0.9 (0.5 to 1.8)	-0.01 (-0.14 to 0.1)		
Andersson, 1983[94] Moderate	Metoprolol 200mg once daily ("Durules")	Patients' subjective judgment of their migraine: slight	7/34 [20.6%]	10/37 [27.0%]	0.8 (0.3 to 1.8)	-0.06 (-0.26 to 0.1)		
Freitag, 1984[95] Low	**Nadolol 80mg to 240mg/day**	**Treatment successful: Frequency**	**6/24 [25.0%]**	**0/8 [0.0%]**	**4.7 (0.3 to 75.0)**	**0.25 (0.02 to 0.5)**	**4 (2 to 45)**	**250 (22 to 478)**

Appendix Table 50. Efficacy of beta-blockers in prevention of migraine in adults; results from randomized controlled clinical trials (sorted by drug name) (continued)

Reference Risk of bias	Drug and dose	Outcome	Events/ Randomized [Rate of outcome with drug, %]	Events/ Randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
	Nadolol 80mg to 240mg/day	**Treatment successful: Intensity**	**7/24 [29.2%]**	**0/8 [0.0%]**	**5.4 (0.3 to 85.3)**	**0.29 (0.06 to 0.5)**	**3 (2 to 17)**	**292 (58 to 525)**
	Nadolol 80mg to 240mg/day	**Treatment successful: Pain**	**7/24 [29.2%]**	**0/8 [0.0%]**	**5.4 (0.3 to 85.3)**	**0.29 (0.06 to 0.5)**	**3 (2 to 17)**	**292 (58 to 525)**
	Nadolol 80mg to 240mg/day	**Treatment successful: Relief**	**10/24 [41.7%]**	**0/8 [0.0%]**	**7.6 (0.5 to 116.2)**	**0.42 (0.17 to 0.7)**	**2 (2 to 6)**	**417 (172 to 661)**
Briggs, 1979[89] Moderate	Timolol 10mg twice a day	Completely relieved of migraine	2/14 [14.3%]	0/14 [0.0%]	5.0 (0.3 to 95.6)	0.14 (-0.07 to 0.4)		
Stellar, 1984[76] Moderate	**Timolol 10mg twice a day**	**Responders (Patients with 50% or greater reduction in headache frequency)**	**25/47 [53.2%]**	**10/47 [21.3%]**	**2.5 (1.4 to 4.6)**	**0.32 (0.13 to 0.5)**	**3 (2 to 7)**	**319 (135 to 504)**
	Timolol 10mg twice a day	**Global response of great or moderate improvement**	**35/47 [74.5%]**	**12/47 [25.5%]**	**2.9 (1.7 to 4.9)**	**0.49 (0.31 to 0.7)**	**2 (2 to 3)**	**489 (313 to 666)**
	Timolol 10mg twice a day	**Patient rating of medication as extremely or moderately helpful**	**32/47 [68.1%]**	**12/47 [25.5%]**	**2.7 (1.6 to 4.5)**	**0.43 (0.24 to 0.6)**	**2 (2 to 4)**	**426 (243 to 608)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D51. Efficacy of beta-blockers on migraine severity in adults; results from randomized controlled clinical trials (sorted by drug name)

Reference Risk of bias	Drug and dose	Outcome	Events/ randomized [Rate of outcome with drug, %]	Events/ Randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
Andersson, 1983[94] Moderate	**Metoprolol 200mg/day**	**50% reduction in sum of severity score**	**10/34 [29.4%]**	**4/37 [10.8%]**	**2.7 (0.9 to 7.9)**	**0.19 (0.00 to 0.4)**	**5 (3 to 326)**	**186 (3 to 369)**
	Metoprolol 200mg/day	**1-50% reduction in the sum of severity score**	**15/34 [44.1%]**	**8/37 [21.6%]**	**2.0 (1.0 to 4.2)**	**0.22 (0.01 to 0.4)**	**4 (2 to 85)**	**225 (12 to 438)**
Sjaastad, 1972[86] Moderate	Pindolol (LB-46) 7.5 to 15mg	50% reduction in headache indices	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)		

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D52. Efficacy of beta-blockers for migraine prevention in adults on intermediate outcomes of migraine frequency, duration, and severity (results from randomized controlled clinical trials) (sorted by drug name)

Reference Risk of bias	Drug, dose	Outcome	Randomized into drug/placebo groups	Mean difference (95% CI)
Ekbom, 1975[87] Moderate	Alprenolol 200mg/day ("Durules")	Migraine attacks per week	33/33	0.2 (-0.9 to 1.3)
	Alprenolol 200mg/day ("Durule")	Headache index per week	33/33	0.2 (-1.7 to 2.1)
Kangasneimi, 1987[97] Moderate	Metoprolol 200mg once daily ("Durules")	Day with migraine per 4 weeks	77/77	0.7 (0.1 to 1.1)
Andersson, 1983[94] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Mean number of migraine days**	**34/37**	**-2.1 (-3.8 to -0.5)**
Kangasneimi, 1987[97] Moderate	Metoprolol 200mg once daily ("Durules")	Day with migraine per 4 weeks: aura attacks	77/77	0.8 (0.0 to 0.7)
	Metoprolol 200mg once daily ("Durules")	**Mean duration (h) per attack: total**	**77/77**	**2.0 (0.2 to 2.9)**
	Metoprolol 200mg once daily ("Durules")	Mean duration (h) per attack: aura attacks	77/77	1.3 (-0.3 to 2.5)
	Metoprolol 200mg once daily ("Durules")	Attack frequency per 4 weeks: total	77/77	0.7 (0.2 to 1.0)
Andersson, 1983[94] Moderate	Metoprolol 200mg once daily ("Durules")	Mean attack frequency	34/37	-1.5 (-2.4 to -0.6)
Siniatchkin, 2007[99] Moderate	Metoprolol 200mg once daily ("Durules")	Frequency of migraine attacks	10/10	-0.9 (-2.2 to 0.4)
			Pooled	-0.5 (-2.1 to 1.1)
Kangasneimi, 1987[97] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Attack frequency per 4 weeks: aura attacks**	**77/77**	**0.6 (0.1 to 0.6)**
	Metoprolol 200mg once daily ("Durules")	**Sum of intensity score per 4 weeks: total**	**77/77**	**0.9 (0.7 to 2.4)**
	Metoprolol 200mg once daily ("Durules")	**Sum of intensity score per 4 weeks: aura attacks**	**77/77**	**1.2 (0.3 to 1.8)**
	Metoprolol 200mg once daily ("Durules")	**Mean intensity score per attack: total**	**77/77**	**0.1 (0.1 to 0.4)**
	Metoprolol 200mg once daily ("Durules")	Mean intensity score per attack: aura attacks	77/77	0.0 (-0.1 to 0.4)
Andersson, 1983[94] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Sum of severity score (migraine days' intensity) 1=Annoying, but patient not disabled; 2=Patient pertly disabled (affecting his/her ability to work); and 3=Patient disabled -unable to work or in bed)**	**34/37**	**-4.6 (-8.2 to -0.9)**

Appendix Table 52. Efficacy of beta-blockers for migraine prevention in adults on intermediate outcomes of migraine frequency, duration, and severity (results from randomized controlled clinical trials) (sorted by drug name) (continued)

Reference Risk of bias	Drug, dose	Outcome	Randomized into drug/placebo groups	Mean difference (95% CI)
Kangasneimi, 1987[97] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Sum of global ratings per 4 weeks: total**	**77/77**	**4.1 (1.3 to 6.4)**
	Metoprolol 200mg once daily ("Durules")	**Sum of global ratings per 4 weeks: aura attacks**	**77/77**	**3.6 (0.7 to 5.5)**
	Metoprolol 200mg once daily ("Durules")	**Mean global rating (1-10) per attack: total**	**77/77**	**1.0 (0.2 to 1.3)**
	Metoprolol 200mg once daily ("Durules")	**Mean global rating (1-10) per attack: aura attacks**	**77/77**	**0.6 (0.2 to 1.5)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per 4 weeks: aura attacks**	**77/77**	**0.8 (0.2 to 2.9)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per attack: total**	**77/77**	**1.0 (0.2 to 1.0)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per attack: aura attack**	**77/77**	**0.5 (0.1 to 0.8)**
	Metoprolol 200mg once daily ("Durules")	Consumption of ergotamine tablets per 4 weeks: total	77/77	1.5 (0.0 to 2.1)
	Metoprolol 200mg once daily ("Durules")	Consumption of ergotamine tablets per 4 weeks: aura attacks	77/77	1.5 (-0.4 to 1.4)
Andersson, 1983[94] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Acute tablet consumption**	**34/37**	**-9.3 (-16.4 to -2.2)**
Kangasneimi, 1987[97] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Consumption of analgesic tablets per 4 weeks**	**77/77**	**2.5 (0.5 to 4.8)**
			Pooled	-2.9 (-14.5 to 8.6)
Sjaastad, 1972[86] Moderate	Pindolol (LB-46) 7.5 to 15mg	Headache days	28/28	0.5 (-2.3 to 3.4)
	Pindolol (LB-46) 7.5 to 15mg	Headache indices	28/28	-0.1 (-4.5 to 4.3)
Briggs, 1979[89] Moderate	Timolol 10mg twice a day	Headache frequency	14/14	1.6 (-1.2 to 4.4)
	Timolol 10mg twice a day	**Headache frequency**	**14/14**	**3.1 (0.2 to 5.9)**

Results are significant if p value is less than 0.5, 95%CI of mean difference do not include 0, or 95% CI of relative measure of the association do not include 1
Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D53. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults

Examined drug	Reference, Total sample size Number of analyzed % women	Definition of migraine % of patients without aura	Baseline monthly migraine frequency	Eligible age Mean age of subjects	Duration of migraine Prior treatment
Amitriptyline	Couch, 1979[100] Sample 116 Analyzed 100 % women 84	Modified 1962 Ad Hoc National Institutes of Health Committee NR	NR	15-60 NR	NR NR
Amitriptyline	Gomersall, 1973[101] Sample 26 Analyzed 20 % women 75	Ad hoc committee NR	NR	NR 21-30 years old:1, 31-40 years old:4, 41-50 years old:11, 51-60 years old:2, 61-70 years old:2	1-10 yr:5, 11-20 yr:5, 21-30 yr:6, 31-40:2, 41-50:2 NR
Amitriptyline	Mathew, 1981[102] Sample 715 Analyzed 554 % women 94.5	NR NR	NR	NR (age ranged from 19-57) Mean: 38	NR NR
Amitriptyline	Bank, 1994[103] Sample 64 Analyzed 51 % women 73.4	International Headache Society 81.25	HUI=0.16, HUIc=0.24	NR 34	At least 12 months NR
Amitriptyline	Oguzhanoglu, 1999[104] Sample 17 Analyzed 15 % women 80	International Headache Society NR	NR	NR 31	NR NR
Amitriptyline	Krymchantowski, 2002[105] Sample 39 Analyzed 27 % women 66.7	NR NR	NR	NR 36.4	NR 100% overusing symptomatic medications
Amitriptyline	Bulut, 2004[106] Sample 76 Analyzed 52 % women 84.6	International Headache Society 77	Yes	16-50 31.9	NR NR
Amitriptyline	Lampl, 2009[107] Sample 132 Analyzed 132 % women 73	International Headache Society 76	Yes	18-60 32	16y NR

Appendix Table 53. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults (continued)

Examined drug	Reference, Total sample size Number of analyzed % women	Definition of migraine % of patients without aura	Baseline monthly migraine frequency	Eligible age Mean age of subjects	Duration of migraine Prior treatment
Amitriptyline	Couch, 2011[108] Sample 391 Analyzed 317 % women 81	Modified 1962 Ad Hoc National Institutes of Health Committee NR	NR	18-70 34.9	NR NR
Amitriptyline	Couch, 1976[109] Sample 114 Analyzed 73 % women 84.9	Not specified NR	NR	NR NR	NR NR
Amitriptyline	Rafieian-Kopaei, 2005[62] Sample 105 Analyzed 95 % women NR	International Headache Society NR	Mean attack frequency: 4.02 (per month)	Adolescent & Adults NR	>1 (from inclusion criteria) NR
Amitriptyline	Rafieian-Kopaei, 2005[62] Sample 105 Analyzed 95 % women NR	International Headache Society NR	4.02 migraine attacks per month, 25.12 h average duration	15-45 NR	At least 12 months NR
Femoxetine	Orholm, 1986[110] Sample 65 Analyzed 53 % women 84.9	Paroxysmal headache associated with discomfort, possibly with inability to work, and at least one of the following symptoms: nausea, vomiting, visual disturbances and parasthesia NR	Yes	NR >=50 years old= 12; 30-50 years old= 38; <30 years old =3	NR NR
Femoxetine	Zeeberg, 1981[111] Sample 59 Analyzed 45 % women 86.7	Paroxysmal headache associated with discomfort, possibly with inability to work, and at least one of the following symptoms: nausea, vomiting, visual disturbances and parasthesia NR	Yes	NR >=50 years old= 9; 30-50 years old =29; <30 years old= 7	NR NR
Femoxetine	Kangasniemi, 1983[75] Sample 29 Analyzed 24 % women 86.2	NR NR	Yes	NR 37	NR NR

Appendix Table 53. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults (continued)

Examined drug	Reference, Total sample size Number of analyzed % women	Definition of migraine % of patients without aura	Baseline monthly migraine frequency	Eligible age Mean age of subjects	Duration of migraine Prior treatment
Femoxetine	Orholm, 1985[112] Sample 59 Analyzed 47 % women NR	NR NR	NR	NR NR	NR NR
Fluoxetine	Adly, 1992[113] Sample 32 Analyzed 18 % women 83.3	the Ad hoc Committee on Classification of headache NR	Headache score 33.5	NR 37.5	NR 2 amitriptyline or nadolol, 1 imipramine
Fluoxetine	Saper, 1994[114] Sample 111 Analyzed 111 % women 87.4	International Headache Society NR	NR	18-60 36.6	At least 24 months NR
Fluoxetine	Steiner, 1998[115] Sample 53 Analyzed 49 % women 75.5	NR 54.8	Yes	18-45 40.6	NR NR
Fluoxetine	d'Amato, 1999[116] Sample 52 Analyzed 52 % women 63.5	International Headache Society 1988 criteria 100	NR	18-65 37.6	At least 6 months NR
Mianserin	Monro, 1985[117] Sample 38 Analyzed 34 % women NR	NR NR	NR	18-65 NR	NR NR
Tonabersat	Goadsby, 2009[118] Sample 124 Analyzed 124 % women 92.3	International Headache Society NR	Yes	18-55 36	NR NR
Venlafaxine	Ozyalcin, 2005[119] Sample 60 Analyzed 49 % women 90	International Headache Society 100	Yes	18-70 placebo 38.16; V75 34.25; V150 37.19	NR NR
Venlafaxine	Tarlaci, 2009[120] Sample 105 Analyzed 93 % women 81.7	International Headache Society 93.5	Yes	NR 31.4	NR NR

NR – not reported

Appendix Table D54. Funding and conflict of interest in randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Couch, 1979[100]	Industry	No	Yes	NR	NA
Gomersall, 1973[101]	Industry	No	Yes	NR	NA
Mathew, 1981[102]	NR	NR	NR	NR	NR
Bank, 1994[103]	NR	No	Yes	NR	NA
Oguzhanoglu, 1999[104]	NR	No	NR	NR	NA
Krymchantowski, 2002[105]	No	No	Yes	NR	NA
Bulut, 2004[106]	Industry	Yes	Yes	NR	NA
Lampl, 2009[107]	No	Yes	Yes	Yes	Dr. Lampl received personal compensation from Glaxo, Pfizer Austria, Mundipharma, Gru¨ nenthal, Bayer-Shering, Biogen Idec and Astra Zeneca. Dr. Huber has nothing to disclose. Dr. Adl has nothing to disclose. Dr. Luthringshausen has nothing to disclose. Dr. Franz has nothing to disclose. Dr. Marecek has nothing to disclose. Dr. Weber has nothing to disclose. Dr. Baumhackl has nothing to disclose. Dr. Mueller has nothing to disclose.
Couch, 2011[108]	Industry	Yes	Yes	NR	NA
Couch, 1976[109]	No	No	NR	NR	NA
Rafieian-Kopaei, 2005[62]	Other	NR	Yes	NR	All authors are from the the University that sponsored the study
Rafien-Kopaei, 2005[62]	University	No	Yes	NR	NA
Orholm, 1986[110]	No	Yes	Yes	NR	NA
Zeeberg, 1981[111]	No	Yes	Yes	NR	NA
Kangasniemi, 1983[75]	No	No	NR	NR	NA
Orholm, 1985[112]	NR	NR	NR	NR	NA
Adly, 1992[113]	NR	No	Yes	NR	NA
Saper, 1994[114]	Industry	Yes	Yes	NR	NA
Steiner, 1998[115]	Industry	Yes	Yes	NR	NA
d'Amato, 1999[116]	NR	Yes	Yes	NR	NA
Monro, 1985[117]	Industry	No	Yes	NR	NA
Goadsby, 2009[118]	Industry	No	Yes	NR	JGM is an employee of Minster Research Ltd
Ozyalcin, 2005[119]	Industry	Yes	Yes	NR	NA
Tarlaci, 2009[120]	No	No	NR	NR	NA

NA – Not applicable; NR – Not reported

Appendix Table D55. Risk of bias in randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults

Reference	Masking of treatment status	Planned intention to treat analysis	Allocation concealment	Adequacy of randomization	Adequacy of randomization (migraine characteristics)	Selective outcome reporting	Risk of Bias
Couch, 1979[100]	DB	No	NR	Yes	Unclear	Unclear	Moderate
Gomersall, 1973[101]	DB	No	Unclear	Unclear (crossover trial)	Unclear (crossover trial)	Unclear	Moderate
Mathew, 1981[102]	Open-label	No	Unclear	Yes	NR	Unclear	High
Bank, 1994[103]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Oguzhanoglu, 1999[104]	Open	No	Unclear	Unclear	F & S	Unclear	Moderate
Krymchantowski, 2002[105]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Bulutm 2004[106]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Lampl, 2009[107]	open	Yes	NR	Yes	F & S	Unclear	Moderate
Couch, 2011[108]	DB	No	NR	Yes	F & S	Unclear	Moderate
Couch, 1976[109]	DB	No	Unclear	NR	NR	Unclear	Moderate
Rafieian-Kopaei, 2005[62]	DB	No	Unclear	NR	F	Unclear	Moderate
Rafieian-Kopaei, 2005[62]	DB	No	NR	Unclear	S	Unclear	Moderate
Orholm, 1986[110]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Zeeberg, 1981[111]	DB	No	Unclear	Yes	F & S	Unclear	Moderate
Kangasniemi, 1983[75]	DB	No	Unclear	NR	NR	Unclear	Moderate
Orholm, 1985[112]	DB	No	NR	Yes	F & S	Unclear	Moderate
Adly, 1992[113]	DB	No	Unclear	Yes	S	Unclear	Moderate
Saper, 1994[114]	DB	No	NR	Yes	S	Unclear	Moderate
Steiner, 1998[115]	DB	No	NR	No	No for F, but S is OK	Unclear	High
d'Amato, 1999[116]	DB	No	NR	Yes	S	Unclear	Moderate
Monro, 1985[117]	DB	No	Unclear	No	Unclear	Unclear	High
Goadsby, 2009[118]	DB	Yes	NR	Yes	F & S	Unclear	Low
Ozyalcin, 2005[119]	DB	No	Unclear	Yes	Unclear	Unclear	Moderate
Tarlaci, 2009[120]	NR (seems open)	Yes	NR	No	F	Unclear	High

DB – double–blind
NR – not reported
F - migraine frequency
S – migraine severity
D – migraine duration

Appendix Table D56. Randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference Sample Analyzed % women	Definition of migraine Years of migraine	Age of subjects	Baseline migraine status
Markley, 1984[121] Sample 20 Analyzed 14 % women 86	"Standard criteria" confirmed by self assessment questionnaire Years of migraine- Chronic headaches for an average of 13.4 years	20 to 50 year Mean age 33 years	57% had no significant relief when treated in the past with drugs used for migraine prophylaxis
Leandri, 1990[122] Sample 30 Analyzed 30 % women 73	IHS criteria Years of migraine, mean: 7.9 +/- 6.2 years	Not reported Not reported	Mean frequency: 4.26 +/- 3.03, mean intensity: 2.60 +/- 0.49, mean duration: 35.76 +/- 21.69, index a (monthly number x mean intensity of attacks): 12.61 +/- 10.96, index b (monthly number x mean intensity x mean duration of attacks): 351.88 +/- 214.84
Gelmers, 1983[123] Sample 60 Analyzed 50 % women 62	Ad Hoc Committee of the NINDS of classic or common migraine Years of migraine- 20 years	Not reported Mean (SD): 30 (9)	Classic migraine active: 8, class migraine placebo: 4, common migraine active: 20, common migraine placebo: 18, age at migraine onset active: 11 (9), age at migraine onset placebo: 10 (8), migraine index active: 56 (25), migraine index placebo: 72 (39)
Migraine-Nimodipine European Study Group, 1989[124] Sample 192 Analyzed 192 % women 78	Ad hoc committee on headache classification of the National Institute of Health Years of migraine, active: 16, placebo 17	Age 18-60 Mean: active 38, placebo 38.3 years	Median duration of migraine in years, active: 16, placebo: 17; migraine days per 4 weeks, active: 4.5, placebo: 4.2; migraine index of days per 4 weeks times severity, active: 9.27, placebo 8.79
McArthur, 1989[125] Sample 24 Analyzed 14 % women Not reported	Ad hoc committee on the classification of headache Years of migraine Not reported	Not reported Not reported	Not reported
Solomon, 1983[126] Sample 23 Analyzed 12 % women 75	Classic or common migraine by ad hoc committee on classification of headache Years of migraine Not reported	Age 19-60 Mean 38.9 years	7/12 (58%) had common migraine and 5/12 (42%) had classic migraine
Meyer, 1983[127] Sample 35 Analyzed 35 % women 66	Ad hoc committee Years of migraine Not reported	Age 20 years and older Mean 39.6 (12.1) years	27/35 (77%) patients with migraine, common migraine: 14/35 (40%), classic migraine: 13/35 (37%), cluster headaches: 8/35 (23%)

Appendix Table 56. Randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults (continued)

Reference Sample Analyzed % women	Definition of migraine Years of migraine	Age of subjects	Baseline migraine status
Havanka-Kanniainen, 1985[128] Sample 33 Analyzed 29 % women 85	Ad hoc committee Years of migraine- Mean duration of 14 years (1.6)	Not reported Mean age 32 (1.3)	20/30 (67%) with classical migraine, 33% with common,
Migraine-Nimodipine European Study Group, 1989[129] Sample 89 Analyzed 72 % women 79	National Institute of Health for classic migraine Years of migraine- Active: 15 years, control: 10 years	18-60 Mean age active: 33.2 yrs, control: 34.8 yrs	Migraine days/4 weeks active: 3.4, control: 3.4; migraine index active: 7.7, control: 8.1
Ansell, 1988[130] Sample 68 Analyzed 57 % women 71	Defined in accordance with the definition of the research group on migraine and headache of the world federation of neurology, 1969 Years of migraine- Not reported	18-60 Not reported	Placebo group: 16 common migraine, 11 classical migraine; active group: 14 with common migraine and 14 with classical migraine
Shukla, 1995[131] Sample 36 Analyzed 28 % women 79	International Headache Society Years of migraine- 8.8 (1.18) years	15-45 Mean years: 29.8 (1.89)	Frequency: 10.4 (1.76), mild severity 0/28, moderate severity 12/28, severe severity 16/28, 100% with nausea/vomiting

Appendix Table D57. Funding and conflict of interest in randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference	Sponsorship	Ethical approval of study	Consent of participants	Conflict of interest
Markley, 1984[121]	Industry (Knoll Pharmaceutical) provided medication	Not reported	Yes	Not reported
Leandri, 1990[122]	Industry (Sandoz Prodotti Farmaceutici supplied medications)	Not reported	Yes	Not reported
Gelmers, 1983[123]	Not reported	Not reported	Yes	Not reported
Migraine-Nimodipine European Study Group, 1989[124]	Not reported	Not reported	Not reported	Not reported
McArthur, 1989[125]	Industry (Pfizer) and not for profit (national migraine foundations)	Not reported	Yes	Not reported
Solomon, 1983[126]	Industry (Knoll Pharmaceutical) provided medication	Not reported	Yes	Not reported
Meyer, 1983[127]	Grant from government	Yes	Yes	Not reported
Havanka-Kanniainen, 1985[128]	Industry (Bayer Ltd supplied medications)	Yes	Yes	Not reported
Migraine-Nimodipine European Study Group, 1989[129]	Not reported	Not reported	Not reported	Not reported
Ansell, 1988[130]	Not reported	Not reported	Yes	Not reported
Shukla, 1995[131]	Not reported	Not reported	Yes	Not reported

Appendix Table D58. Risk of bias in randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Markley, 1984[121]	double blind	No	Unclear	Not reported	No	Moderate
Leandri, 1990[122]	double blind	No	Unclear	Yes	No	Moderate
Gelmers, 1983[123]	double blind	No	Unclear	Yes	No	Moderate
Migraine-Nimodipine European Study Group, 1989[124]	double blind	Yes	Unclear	No, migraine index different between nimodipine and placebo groups	No	Moderate
McArthur, 1989[125]	double blind	No	Unclear	No, migraine index different between nimodipine and placebo groups	No	High
Solomon, 1983[126]	double blind	no	Unclear	Unclear	No	Moderate
Meyer, 1983[127]	double blind	No	Unclear	Unclear	No	Moderate
Havanka-Kanniainen, 1985[128]	double blind	No	Unclear	Unclear	No	Moderate
Migraine-Nimodipine European Study Group, 1989[129]	double blind	Yes	Unclear	Yes	No	Low
Ansell, 1988[130]	double blind	No	Unclear	Unclear, more classical migraine in active group	No	Moderate
Shukla, 1995[131]	double blind	No	Unclear	Unclear	No	Moderate

Appendix Table D59. Randomized controlled clinical trials that examined ACE inhibitors or Angiotensin II receptor blockers for migraine prevention in adults

Active drug	Reference Sample Analyzed % women	Definition of migraine Years of migraine	Eligible age of subjects	Baseline migraine status
Lisinopril	Schrader, 2001[132] Sample 60 Analyzed 55 % women 81	IHS criteria Years of migraine Not reported	Age 18 to 60 years gender, mean (SD): women, 41 (9), men, 43 (5) years	Mean (SD); hours with headache: 65(74), days with headache 9.4(4.0), days with migraine 6.8(3.0)
Captropril	Minervini, 1987[133] Sample 12 Analyzed 12 % women 58	Ad Hoc committee on the classification of headache Years of migraine 7-36 years	Not reported 35-64	Not reported
Candesartan	Tonvik, 2003[134] Sample 60 Analyzed 57 % women 79	IHS criteria Years of migraine Not reported	Age 18 to 65 years mean (SD) women: 42(11), men: 48(12)	Migraine days 5.7 (2.9) Disability level 9.7 (6.4) Sick leave days 1.00 (2.00)
Telmisartan	Diener, 2009[135] Sample 84 Analyzed 84 % women 84.5	International Headache Society Years of migraine Not reported	18-65 Active group: 39.8 (11.7), placebo: 41.6 (12.9) years	Migraine days active: 6.2 (2.9), placebo: 7.6 (3.7); headache hours active: 58.2 (50.4), placebo: 74.4 (64.2)

Appendix Table D60. Funding and conflict of interest in randomized controlled clinical trials that examined ACE inhibitors or Angiotensin II receptor blockers for migraine prevention in adults

Reference	Sponsorship	Ethical approval of study	Consent of participants	Conflict of interest	Disclosed relationships
Schrader, 2001[132]	Industry by AstraZeneca	Yes	Yes	Yes	HS and GB have been reimbursed by AstraZeneca, one of the manufacturers of lisinopril, for attending conferences. These conferences were unrelated to the present study.
Minervini, 1987[133]	Not reported	Not reported	Not reported	Not reported	Not applicable
Tronvik, 2003[134]	Industry by AstraZeneca	Yes	Yes	Yes	Dr. Tronvik has been reimbursed by AstraZeneca for attending a conference unrelated to the present study.
Diener, 2009[135]	By industry (Boehringer Ingelheim)	Yes	Yes	Yes	Multiple authors with honoraria or past research funding with pharmaceutical industry

Appendix Table D61. Risk of bias in randomized controlled clinical trials that examined ACE inhibitors or Angiotensin II receptor blockers for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Schrader, 2001[132]	double blind	Yes	Adequate	Not reported	No	Low
Minervini, 1987[133]	double blind	Unclear	Unclear	Unclear	No	Low
Tronvik, 2003[134]	double blind	Yes	Adequate	Not reported	No	Low
Diener, 2009[135]	double blind	No	Unclear	Headache hours greater in placebo group at baseline	No	High

Appendix Table D62. Randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference Sample Analyzed % women	Definition of migraine Years of migraine	Eligible age of subjects	Baseline migraine status
Ryan, 1975[136] Sample 75 Analyzed 75 % women 80	Common or classical migraine Years of migraine Not reported	21-60 Not reported	17 tyramine positive, 58 tyramine negative
Ryan, 1975[137] Sample 133 Analyzed 133 % women 78	Not reported Years of migraine Median duration 22 years	Not reported Median age 41 years	4/133 (3%) had migraine related to menses, 32/133 (24%) had migraine related to emotional stress
Shafar, 1972[138] Sample 65 Analyzed 50 % women 84	Not reported Years of migraine Not reported	Not reported Median age females=48 years, median age males=45 years	Not reported
Stensrud, 1976[139] Sample 29 Analyzed 27 % women 83	Not reported Years of migraine Not reported	Not reported Mean 45.4 years	Mean number of headache days at baseline: 5.78, mean headache index at baseline: 10.67
Martucci, 1985[140] Sample 20 Analyzed 20 % women 70	Ad hoc committee classification system Years of migraine All participants had a clinical history longer than 5 years	Not reported Mean age 32.5 years	Not reported
Denaro, 1985[141] Sample 20 Analyzed 20 % women 70	Ad hoc committee classification system Years of migraine All participants had a clinical history longer than 5 years	Not reported Mean age 32.5 years	Not reported
Boisen, 1978[142] Sample 71 Analyzed 49 % women Not reported	Migraine was defined as paroxysmal headache associated with discomfort, possibly with inability to work, and one or more of the following symptoms: nausea, vomiting, visual disturbances and paresthesia Years of migraine Not reported	16 to 60 years Not reported	7/49 had 4 migraine days monthly, 20/49 had 4-8 days with migraine, 21/49 had more than 8 days with migraine in past two months
Wilkinson, 1970[143] Sample 27 Analyzed 24 % women 89	Not reported Years of migraine Not reported	Over 16 years of age Average age of men: 38, of women: 37.5	Not reported
Adam, 1978[144] Sample 96 Analyzed 70 % women 84.3	Not reported Years of migraine Not reported	Not reported Mean age group one (clonidine to placebo) 40 years; mean age group two (placebo to clonidine) 35 years	Less than 3 headaches per 3 months 24/70 (34%), more than 3 headaches per 3 months 46/70 (66%)

Appendix Table 62. Randomized controlled clinical trials that examined clomidine for migraine prevention in adults (continued)

Reference Sample Analyzed % women	Definition of migraine Years of migraine	Eligible age of subjects	Baseline migraine status
Bredfeldt, 1989[145] Sample 43 Analyzed 30 % women 80	Ad hoc committee on the classification of headache Years of migraine Not reported	18 years or more Range 20-57 years	Not reported
Kallanranta, 1977[146] Sample 50 Analyzed 50 % women 72	Not reported Years of migraine Not reported	Not reported mean age 31.6 years	24/50 (48%) with classic migraine, 26 (52%) with common migraine, 6/50 (12%) with dietary migraine, mean frequency of attacks was 3.94 (sd 2.19)
Kallanranta, 1977[146] Sample 50 Analyzed 50 % women 64	Not reported Years of migraine Not reported	Not reported Mean age 36.3 years	14/50 (28%) with classic migraine, 36/50 (72%) with common migraine, 3/50 (6%) with dietary migraine, mean frequency of attacks was 4 (sd 2.20)
Das, 1979[147] Sample 20 Analyzed 20 % women 70	Ad hoc committee on classification of headache Years of migraine Not reported	Not reported 20-48 years	Not reported

Appendix Table D63. Sponsorship and conflict of interest in randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference	Sponsorhsip	Ethical approval of study	Consent of participants	Conflict of interest
Ryan, 1975[136]	Not reported	Not reported	Not reported	Not reported
Ryan, 1975[137]	Not reported	Not reported	Not reported	Not reported
Shafar, 1972[138]	Not reported	Not reported	Yes	Not reported
Stensrud, 1976[139]	Not reported	Not reported	Not reported	Not reported
Martucci, 1985[140]	Not reported	Not reported	Yes	Not reported
Denaro, 1985[141]	Not reported	Not reported	Yes	Not reported
Boisen, 1978[142]	Not reported	Not reported	Yes	Not reported
Wilkinson, 1970[143]	Not reported	Not reported	Yes	Not reported
Adam, 1978[144]	Industry (Boehringer Ingelheim Limited)	Not reported	Yes	Not reported
Bredfeldt, 1989[145]	Industry (Boehringer Ingelheim Pharmaceuticals)	Not reported	Yes	Not reported
Kallanranta, 1977[146]	Not reported	Not reported	Not reported	Not reported
Kallanranta, 1977[146]	Not reported	Not reported	Not reported	Not reported
Das, 1979[147]	Industry (Unichem Labs supplied medication)	Not reported	Not reported	Not reported

Appendix Table D64. Risk of bias in randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Ryan, 1975[136]	double blind	Unclear	Unclear	Unclear	No	Low
Ryan, 1975[137]	double blind	Unclear	Unclear	Unclear	No	Low
Shafar, 1972[138]	double blind	No	Unclear	Unclear	No	Moderate
Stensrud, 1976[139]	double blind	No	Unclear	Unclear	No	Moderate
Martucci, 1985[140]	double blind	Unclear	Unclear	Unclear	No	Low
Denaro, 1985[141]	double blind	Unclear	Unclear	Unclear	No	Low
Boisen, 1978[142]	double blind	No	Unclear	Unclear	No	Moderate
Wilkinson, 1970[143]	double blind	No	Unclear	Unclear	Unclear, different dosages of clonidine not reported separately	Moderate
Adam, 1978[144]	double blind	No	Unclear	Yes	No	Moderate
Bredfeldt, 1989[145]	double blind	No	Unclear	Unclear	No	High
Kallanranta, 1977[146]	Not reported	Unclear	Unclear	Unclear	No	Unclear
Kallanranta, 1977[146]	Not reported	Unclear	Unclear	Unclear	No	Unclear
Das, 1979[147]	double blind	Unclear	Unclear	Unclear	No	Low

Appendix Table D65. Randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference Sample Analyzed % women	Definition of migraine % without aura	Baseline severity	Eligible age Age of subjects	Duration of migraine Prior treatment (exposure) history
Martucci, 1983[148] Sample 90 Analyzed 79 % women 60	Common migraine (Ad Hoc Committee on Classification of Headache) 100 (assumed)	NR	Adults & Middle aged Mean: 36.6	NR NR
Herrmann, 1977[149] Sample 153 Analyzed unclear % women 73.2	NR 32.5 (assumed)	NR (Median frequency lies around 7-10 attacks per month)	NR NR (median lies around 20-40)	<1y: 6.8%, 1-5y: 35.8%, 5-10y: 15.9%, 10y: 37% NR
Whewell, 1966[150] Sample 74 Analyzed 50 % women 80	Migraine defined as a periodic throbbing headache, unilateral initially, with at least three of the following features: a) sensory prodromata, b) photophobia, c) nausea or vomiting, d) family history of migraine, and e) fluid retention before or diuresis during attack. NR	≥1 for 4 wks (from exclusion criterion)	Adolescent, Adults & Middle aged Mean: 42	20 NR
Pradalier, 2004[151] Sample 384 Analyzed 363 % women 80.7	Migraine (with or without aura) was based on criteria defined by the International Headache Society 36.9	Mean migraine attacks: 3.3	Adults & Middle aged Mean: 39.1	15.8 NR
Neuman, 1986[152] Sample 40 Analyzed 40 % women 45	Migraine NR	Mean migraine attacks: 3.3	Adults, Middle aged, & Aged Mean: 47	NR NR
Buscaino, 1991[153] Sample 90 Analyzed 90 % women 70	Migraine (Ad Hoc Committee) 100	NR (median lies around 5 to 6 attacks per month")	Adults & Middle aged Mean: 36.8	16 Flunarizine, ergot derivatives, and anti-depressants
Buscaino, 1991[153] Sample 18 Analyzed 13 % women 83.3	Common (n=16), Classic (n=1), Cluster (n=1) 88.9	NR	Adults & Middle aged Mean: 33.2	NR NR
Somerville, 1976[154] Sample 150 Analyzed 132 % women NR	Migraine defined as recurrent paroxysmal headahce lasting a minimum of one hour and associated with at least one of the following symptoms: nausea, vomiting, photophobia, visual, motor or sensory symptoms or dysphasia NR	NR (Median frequency lies around 3-4 attacks per month)	NR NR	NR NR

Appendix Table 65. Randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults (continued)

Reference Sample Analyzed % women	Definition of migraine % without aura	Baseline severity	Eligible age Age of subjects	Duration of migraine Prior treatment (exposure) history
Bonuso, 1983[155] Sample 41 Analyzed unclear % women 68.3	Mixed headache diagnosed in accordance with the definitions of the "ad hoc Committee" 100 (assumed)	NR	Adults & Middle aged NR	NR NR

NR – Not reported

Appendix Table D66. Funding and conflict of interest in randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Martucci, 1983[148]	NR	NR	NR	NR	NR
Herrmann, 1977[149]	NR	NR	Yes	NR	NR
Whewell, 1966[150]	NR	NR	NR	NR	NR
Pradalier, 2004[151]	Industry	Yes	Yes	No	NA
Neuman, 1986[152]	NR	NR	NR	NR	NR
Buscaino, 1991[153]	NR	NR	Yes	NR	NR
Buscaino, 1991[153]	NR	NR	Yes (unclear if it is fully informed, but patients agreed to participate in the study)	NR	NR
Somerville, 1976[154]	NR	NR	NR	NR	NR
Bonuso, 1983[155]	NR	NR	NR	NR	NR

NR – not reported

Appendix Table D67. Risk of bias in randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference	Masking of treatment status	ITT planned	Allocation concealment	Adequacy of randomization	Adequacy of randomization (migraine characteristics)	Selective outcome reporting	Risk of bias
Martucci, 1983[148]	DB	No	Unclear	NR	NR	No	Moderate
Herrmann, 1977[149]	DB	No	Unclear	Yes	F, S & D	Unclear	Moderate
Whewell, 1966[150]	DB	No	Unclear	NR	NR	Unclear	Moderate
Pradalier, 2004[151]	DB	Yes	Unclear	Yes	F & D	No	Low
Neuman, 1986[152]	DB	No	Unclear	Yes	F	Unclear	Moderate
Buscaino, 1991[153]	DB	No	Unclear	Yes	F, S & D	Unclear	Moderate
Buscaino, 1991[153]	DB	No	Unclear	NR	F	Unclear	Moderate
Somerville, 1976[154]	DB	No	Unclear	NR	F	Unclear	Moderate
Bonuso, 1983[155]	NR	No	Unclear	NR	S & D	Unclear	Moderate

F- frequency
S - severity
D - duration
DB – double-blind
NR – not reported

Appendix Table D68. Randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults

Reference	Country	Objective	Sample [Number analyzed] % women	Age	Definition of migraine	Presence of aura % without aura	Duration of migraine, years	Baseline severity	Comorbidity
Millan-Guerrero, 2009[156]	Mexico	Histamine vs. botulinum toxin type A (BoNTA)	100 [100] 92% women	Mean: 33	International Headache Society	Included % without aura 81	15	Mean migraine frequency (days): 4.12	NR
Mathew, 2009[157]	USA	Onabotulinumtoxin A (BOTOX, Allergan, Inc) vs. topiramate (TOPAMAX, Ortho-McNeil)	60 [33] 90% women	Mean: 36.8	Migraine headache with or without aura occurring on >14 days/month for >3 months in the absence of medication overuse	Included % without aura NR	NR	Headache days: 15.6	NR
Magalhaes, 2010[158]	Brazil	Botulinum toxin type A vs. amitriptyline	72 [unclear] 97.2% women	Mean: 34.1	Chronic daily migraines, according to the International Classification of Headache Disorders-II	NR % without aura NR	NR	NR (Number of pain days at baseline: 24)	NR
Cady, 2011[159]	USA	OnabotulinumtoxinA vs. topiramate (CM)	59 [44] 91.5% women	Mean: 39.6	Chronic migraine (CM) fulfilling criteria of the Second Edition of the ICHD	NR % without aura NR	16 (median)	NR (Headache days/month: 21.1)	Every subject reported at least one problem with a body system (58/59, neurological; 39/59. psychological). A physical/neurological abnormality was found in 13.6% (8/59)
Blumenfeld, 2008[160]	USA	Botulinum toxin type A (BoNTA; BOTOX®: Allergan, Inc.) vs. divalproex sodium (DVPX; DEPAKOTE®: Abbott Laboratories)	59 [59] 84.7% women	Mean: 42.4	Episodic migraine (defined for this study as ≥3 migrainous headaches but <15 days /month) or	NR % without aura NR	NR	Number of headache days per month: 11.7	NR

Appendix Table D68. Randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults (continued)

Reference	Country	Objective	Sample [Number analyzed] % women	Age	Definition of migraine	Presence of aura % without aura	Duration of migraine, years	Baseline severity	Comorbidity
					chronic migraine (defined for this study as migrainous headaches on 15 days/month)				

NR – not reported

Appendix Table D69. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults

Reference	Finance	Ethical approval	Consent	Conflict of interest	Conflict of interest disclosure
Millan-Guerrero, 2009[156]	Not reported	Yes	Yes	Not reported	Not applicable
Mathew, 2009[157]	Industry	Yes	Yes	Yes	Dr. Matthew is on the scientific advisory board of Merck, Allergan, and Ortho-McNeil. Hi is also on the speaker's bureau for Merck, GSK, Endo Pharmaceuticals, and Allergan.
Magalhaes, 2010[158]	Government	Yes	Yes	Not reported	Not applicable
Cady, 2011[159]	Not reported	Yes	Yes	Yes	Dr. Roger Cady: Consultant for GlaxoSmithKline, Merck, Ortho-McNeil. Research grants from Allergan, Endo Pharmaceuticals, GlaxoSmithKline, Merck, and Wyeth. Dr. John Porter: Consulting Speakers panel with Novartis, Forest, Biogen, UCB Pharma, Pfizer, TEVA. Dr. Andrew Blumenfeld: Consultant, speaker's bureau, and research grants from Allergan. Dr. Curtis Schreiber and Dr. Kathleen Farmer: None to disclose.
Blumenfeld, 2008[160]	Industry	Yes	Yes	Yes	Dr. Blumenfeld has received honoraria for speaking activities and a research grant from Allergan, Inc. Dr. Schim has received research grants from Allergan, Inc., has been a consultant for Allergan, Inc., and serves on the speaker's bureau for Allergan. He has received research grants from Boehringer, Pfizer, GlaxoSmithKline, Merck, Astra-Zeneca, and Ortho-McNeil. He serves on the speaker's bureau for Boehringer, Pfizer, GlaxoSmithKline, Merck, and Ortho-McNeil. Dr. Chippendale has received personal compensation from Allergan, Inc., and Photothera for consulting services. He received personal compensation from Boehringer Ingelheim, Pfizer, and Teva for speaking.

Appendix Table D70. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults

Reference	Masking	Planned intention to treat analysis	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias	Other concerns
Millan-Guerrero, 2009[156]	Double blind	No	Unclear	Yes	Unclear	Low	Poor reporting quality
Mathew, 2009[157]	Double blind	No	Unclear	No	Unclear	Moderate	
Magalhaes, 2010[158]	Open	No	Unclear	Unclear (age seems to differ by groups; no tests conducted)	Unclear	High	
Cady, 2011[159]	Double blind	No	Unclear	Unclear (unclear in demographic characters, but adequate in migraine characteristics)	Unclear	Moderate	
Blumenfeld, 2008[160]	Double blind	Yes	Unclear	No	Unclear	Moderate	Baseline Headache severity differs by groups

Appendix Table D71. Comparative effectiveness of botox vs. topiramate in migraine prevention (results from individual randomized controlled clinical trials)

Outcome	Reference Risk of bias	Active vs. control drug	Events/ Randomized with active drug	Events/ Randomized with control drug	Relative risk 95% CI)	Absolute risk difference (95% CI)
At least a 50% reduction in headache days per month	Cady, 2011[159] Moderate	Topiramate vs. OnabotulinumtoxinA	12/30	9/29	1.3 (0.6 to 2.6)	0.09 (-0.15 to 0.33)
≥ 50% reduction in HA/migraine days	Mathew, 2009[157] High	Topiramate plus placebo injection vs. OnabotulinumtoxinA (Botox) + Oral placebo	9/30	9/30	1.0 (0.5 to 2.2)	0.00 (-0.23 to 0.23)
Migraine Disability Assessment (MIDAS) total score >21 (severe disability)	Mathew, 2009[157] High	Topiramate plus placebo injection vs. OnabotulinumtoxinA (Botox) + Oral placebo	7/30	6/30	1.2 (0.4 to 3.1)	0.03 (-0.17 to 0.24)
≥ 50% improvement in the Migraine Disability Assessment (MIDAS) total score	Mathew, 2009[157] High	Topiramate plus placebo injection vs. OnabotulinumtoxinA (Botox) + Oral placebo	12/30	11/30	1.1 (0.6 to 2.1)	0.03 (-0.21 to 0.28)
Physician global assessment: marked improvement	Cady, 2011[159] Moderate	Topiramate vs. OnabotulinumtoxinA	10/30	10/29	1.0 (0.5 to 2.0)	-0.01 (-0.25 to 0.23)
Physician global assessment: moderate improvement	Cady, 2011[159] Moderate	Topiramate vs. OnabotulinumtoxinA	6/30	4/29	1.5 (0.5 to 4.6)	0.06 (-0.13 to 0.25)
Physician global assessment: slight improvement	Cady, 2011[159] Moderate	Topiramate vs. OnabotulinumtoxinA	1/30	5/29	0.2 (0.0 to 1.6)	-0.14 (-0.29 to 0.01)
Physician Global Assessment - response to treatment: Marked improvement (defined as at least 75% improvement)	**Mathew, 2009[157] Moderate**	**Topiramate plus placebo injection vs. OnabotulinumtoxinA (Botox) + Oral placebo**	**18/30**	**8/30**	**2.3 (1.2 to 4.4)**	**0.33 (0.10 to 0.57)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D72. Comparative effectiveness of botox vs. divalproex sodium in migraine prevention (results from a single moderate risk of bias individual randomized controlled clinical trial)[161]

Outcome	Active vs. control drug	Events/ randomized with active drug	Events/ randomized with control drug	Relative risk 95% CI)	Absolute risk difference (95% CI)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	2/7	0/7	5.0 (0.3 to 88.5)	0.29 (-0.08 to 0.65)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	2/7	2.0 (0.5 to 7.6)	0.29 (-0.21 to 0.78)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	4/7	1.0 (0.4 to 2.5)	0.00 (-0.52 to 0.52)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	3/7	1.3 (0.5 to 3.9)	0.14 (-0.38 to 0.66)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	5/22	4/23	1.3 (0.4 to 4.2)	0.05 (-0.18 to 0.29)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	10/22	17/23	0.6 (0.4 to 1.0)	**-0.28 (-0.56 to -0.01)**
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	12/22	12/23	1.0 (0.6 to 1.8)	0.02 (-0.27 to 0.32)
≥ 50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	12/22	16/23	0.8 (0.5 to 1.3)	-0.15 (-0.43 to 0.13)
≥ 75% reduction in Migraine Disability Assessment Scores (MIDAS)	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	5/29	16/30	0.3 (0.1 to 0.8)	-0.36 (-0.59 to -0.14)

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D73. Comparative effectiveness of botox vs. amitriptyline in migraine prevention (results from a single high risk of bias individual randomized controlled clinical trial)[158]

Outcome	Active vs. control drug	Events/ randomized with active drug	Events/ randomized with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Physician assessment: improvement	Amitriptyline vs. Botulinum toxin type A	32/37	31/35	1.0 (0.8 to 1.2)	-0.02 (-0.17 to 0.13)
Patient self assessment: improvement	Amitriptyline vs. Botulinum toxin type A	33/37	29/35	1.1 (0.9 to 1.3)	0.06 (-0.10 to 0.22)
Improvement a) any single criterion met among objective criteria: a) a reduction by at least 50% in the number of pain episodes, b) a reduction in the intensity of pain of at least 3 point, and c) a reduction by at least 50% in the number of pain drug doses used for migraine	Amitriptyline vs. Botulinum toxin type A	35/37	31/35	1.1 (0.9 to 1.2)	0.06 (-0.07 to 0.19)
A reduction by at least 50% in the number of pain drug doses used for migraines	Amitriptyline vs. Botulinum toxin type A	26/37	27/35	0.9 (0.7 to 1.2)	-0.07 (-0.27 to 0.13)
A reduction by at least 50% in the number of days of pain	Amitriptyline vs. Botulinum toxin type A	27/37	24/35	1.1 (0.8 to 1.4)	0.04 (-0.17 to 0.25)

CI – confidence interval

Appendix Table D74. Randomized controlled clinical trials of comparative effectiveness of topiramate for migraine prevention in adults (all trials did not report prior migraine preventive treatments)

Reference	Country	Total sample [number analyzed] % females	Age	Definition of migraine	Presence of aura	Duration of migraine	Migraine frequency/ month	Baseline comorbidity
Bartolini, 2005[162]	Italy	49 [44] 70.5% females	Mean 41.8 years	International Headache Society Classification of Head and Facial Pain	Patients having migraine without aura were included in the study	5.45 years	26.6	Not reported
Shaygannejad, 2006[163]	Iran	64 [64] 56.3% females	Mean 34.1 years	International Headache Society criteria	Not reported	11.2 years	5.4	Not reported
Gupta, 2007[164]	India	60 [Variable] 78.3% females	Mean 29.41 years	International Headache Society criteria	31.67% had aura	5.08 years	6.98	30% of patients had premigrainous depression
de Tommaso, 2007[165]	Italy	45 [39] 86.0% females	Mean 37.86 years	Headache Classification Committee, 2004	None of the patients had aura	Not reported	Not reported	Not reported
Millan-Guerrero, 2008[166]	Not reported	90 [90] 86.0% females	Mean 32 years	International Headache Society criteria	With aura (n): Histamine:3, Topiramate: 5, Without aura (n); Histamine: 42, Topiramate: 40	14.8 years	4.1	Not reported
Keskinbora, 2008[167]	Turkey	75 [63] 66.7% females	Mean 37.5 years	International Headache Society criteria	Not reported	Not reported	6.1	BDI-II score: Topiramate: 17.95±5.64, Amitriptyline: 17.05±8.90, Combined: 16.95±6.05
Ashtan, 2008[168]	Iran	62 [60] 81.7% females	Mean 30.5 years	International Headache Society (IHS)	Not reported	At least 1 year	5.9	Not reported
Dodick, 2009[169]	USA	347 [Variable] 84.9% females	Mean 38.8 years	International Headache Society 1.1 or	Not reported	Age at migraine onset:	6.15	Not reported

Appendix Table 74. Randomized controlled clinical trials of comparative effectiveness of topiramate for migraine prevention in adults (all trials did not report prior migraine preventive treatments) (continued)

Reference	Country	Total sample [number analyzed] % females	Age	Definition of migraine	Presence of aura	Duration of migraine	Migraine frequency/ month	Baseline comorbidity
				1.2		20.25 years		
Mohammadianinejad, 2011[170]	Iran	80 [75] 78.8% females	Mean 34.2 years	International Headache Society criteria	Not reported	9.9 years	7.4	Not reported

Appendix Table D75. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of topiramate for migraine prevention in adults

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests - relationship
Bartolini, 2005[162]	Not reported	Yes	Yes	Not reported	Not applicable
Shaygannejad, 2006[163]	Not reported	Yes	Yes	Not reported	Not applicable
Gupta, 2007[164]	Not reported	Yes	Yes	None	Not applicable
de Tommaso, 2007[165]	Not reported	Yes	Yes	Not reported	Not applicable
Millan-Guerrero, 2008[166]	Not reported	Yes	Yes	Not reported	Not applicable
Keskinbora, 2008[167]	Not reported	Yes	Yes	Not reported	Not applicable
Ashtan, 2008[168]	Not reported	Yes	Yes	Not reported	Not applicable
Dodick, 2009[169]	Industry	Yes	Yes	Not reported	Not reported, however, Jim Xiang, Marcia Rupnow, and David Biondi are employees of Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, New Jersey
Mohammadianinejad, 2011[170]	Other	Yes	Yes	None	Not applicable

Appendix Table D76. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of topiramate for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Bartolini, 2005[162]	Open-label	Not reported	Unclear	No (Females were more in the valproate group and males in the topiramate group)	Unclear	High
Shaygannejad, 2006[163]	Double-blind	Yes	Unclear	No (sodium valproate group had slightly more severe headache and lower duration of migraine than topiramate group)	Unclear	Moderate
Gupta, 2007[164]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
de Tommaso, 2007[165]	Double-blind	No	Unclear	Not reported	Unclear	Moderate
Milan-Guerrero, 2008[166]	Double-blind	No	Unclear	Yes	Unclear	Low
Keskinbora, 2008[167]	Double-blind	No	Unclear	Yes	Unclear	Moderate
Ashtari, 2008[168]	Double-blind	No	Unclear	Yes	Unclear	Moderate
Dodick, 2009[169]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mohammadianinejad, 2011[170]	Double-blind	No	Clearly adequate	Yes	Unclear	Moderate

Appendix Table D77. Comparative effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials)

Definition of the outcome	Active drug Daily dose	Control drug Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Decrease in headache days by more than 50%	**Topiramate 100mg**	**Amitriptyline 100mg**	**Dodick, 2009[169] Low**	**97/178 [54.4]**	**74/169 [43.9]**	**1.2 (1.0 to 1.5)**	**0.11 (0.00 to 0.21)**
Decrease in migraine by more than 50%	Topiramate 100mg	Amitriptyline 100mg	Dodick, 2009[169] Low	99/178 [55.6]	78/169 [45.9]	1.2 (1.0 to 1.5)	0.09 (-0.01 to 0.20)
Decrease in headache frequency by more than 50%	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	38/60 [63.0]	28/60 [46.0]	1.4 (1.0 to 1.9)	0.17 (-0.01 to 0.34)
Headache intensity (≥50% reduction in mean migraine intensity)	**Topiramate 25mg BD**	**Lamotrigine 25mg BD**	**Gupta, 2007[164] Low**	**30/60 [50.0]**	**13/60 [21.0]**	**2.3 (1.3 to 4.0)**	**0.28 (0.12 to 0.45)**
Migraine frequency of less than 50% of the basal frequency	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[165] Moderate	8/13 [61.5]	8/15 [53.3]	1.2 (0.6 to 2.2)	0.08 (-0.28 to 0.45)
Reduction of at least 50% in days with headache	Topiramate 75mg/day (25mg in the morning and 50mg in the evening)	Valproate(Slow-release) 750mg/day (250mg in the morning and 500mg in the evening)	Bartolini, 2005[162] High	20/22 [90.9]	21/22 [95.5]	1.0 (0.8 to 1.1)	-0.05 (-0.19 to 0.10)
Decrease in headache frequency by more than 50%	Topiramate 25mg/day, gradually titrated up to 100mg/day	Zonasamide 50mg/day, gradually titrated up to 200mg/day	Mohammadianinejad, 2011[170] Moderate	16/40 [40.0]	15/40 [37.5]	1.1 (0.6 to 1.9)	0.03 (-0.19 to 0.24)
Presence of concomitant symptoms	Topiramate 200mg	Amitriptyline 150mg of 150mg/day)	Keskinbora, 2008[167] Moderate	3/24 [12.5]	8/28 [28.6]	0.4 (0.1 to 1.5)	-0.16 (-0.37 to 0.05)
Presence of concomitant symptoms	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline	Amitriptyline 150mg	Keskinbora, 2008[167] Moderate	5/23 [21.7]	8/28 [28.6]	0.8 (0.3 to 2.0)	-0.07 (-0.31 to 0.17)

Appendix Table 77. Comparative effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials (continued)

Definition of the outcome	Active drug Daily dose	Control drug Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline						
Presence of concomitant symptoms	Topiramate 200mg	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Keskinbora, 2008[167] Moderate	3/24 [12.5]	5/23 [21.7]	0.6 (0.2 to 2.1)	-0.09 (-0.31 to 0.12)

Bold – significant differences at 95% CL

Appendix Table D78. Randomized controlled clinical trials that examined comparative effectiveness of anti-epileptic drugs for migraine prevention in adults

Active vs. control drug	Reference Sample Total Number analyzed % women	Definition of migraine % without aura	Baseline severity	Age of subjects	Years of migraine % with prior preventative treatment
Valproate vs. cinnarizine	Togha, 2008[171] Sample 125 Analyzed: 125 % of women: 80.8	Migraine with or without aura as defined by the International Headache Society % without aura: NR	Mean attack frequency (4 wks): 7.2	16-60 Mean: 34.1	Years of migraine: NR % with prior treatment: 100

NR –not reported

Appendix Table D79. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of anti-epileptic drugs for migraine prevention in adults

Active vs. control drug	Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Valproate vs. cinnarizine	Togha, 2008[171]	NR	Yes	Yes	NR	NR

NR –not reported

Appendix Table D80. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of anti-epileptic drugs for migraine prevention in adults

Reference	Masking of treatment status	Planned intention to treat	Allocation concealment	Adequacy of randomization	Adequacy of randomization (migraine characteristics)	Selective outcome reporting	Risk of bias
Togha, 2008[171]	DB	Yes	Unclear	Yes	F, S & D	No	Low

DB – double-blind
F- frequency
D – duration
S – severity

Appendix Table D81. Migraine frequency and intensity with valproate (600mg/day) vs. cinnarizine (75mg/day) in adults, results from low risk of bias randomized controlled clinical trial[171]

Definition outcomes	Mean [standard deviation] with valproate	Mean [standard deviation] with cinnnarizine	Randomized to valproate/ cinnarizine	Mean difference (95% CI)	Standardized mean difference (95% CI)
Mean attack frequency (4 weeks)	3.0 [1.6]	3.1 [1.7]	67/58	-0.1 (-0.7 to 0.5)	-0.1 (-0.4 to 0.3)
Mean duration of the attack (hours)	9.0 [7.1]	10.0 [7.1]	67/58	-1.0 (-3.5 to 1.4)	-0.1 (-0.5 to 0.2)
Mean intensity of the attack (VAS, 0-10: 0=no pain; 10=worse pain)	5.4 [2.0]	5.0 [1.7]	67/58	0.3 (-0.3 to 1.0)	0.2 (-0.2 to 0.5)
Mean number of days without attack (seems 4 weeks)	26.9 [1.8]	26.9 [1.8]	67/58	0.0 (-0.6 to 0.7)	0.0 (-0.3 to 0.4)
Mean time between two consecutive attack (hours)	12.1 [6.3]	12.3 [6.3]	67/58	-0.2 (-2.4 to 2.0)	0.0 (-0.4 to 0.3)

CI – confidence interval

Appendix Table D82. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
Ashtari, 2008[168] Sample Not reported 81.7% women	To assess the efficacy and safety of low-dose topiramate in migraine prophylaxis vs. propranolol	International Headache Society	Not reported	Mean: 30.8	Mean monthly headache frequency: 5.95
Behan, 1980[172] Sample 56 66.1% women	To compare propranolol with methysergide in a large group of patients with chronic, incapacitating migraine	Chronic, incapacitating migraine	0.5 to 33	Not reported	Not reported; inclusion criterion: at least two attacks of severe migraine per month
Rafieian-Kopaei, 2005[62] Sample 105 % women Not reported	To compare the prophylactic activity of propranolol and amitriptyline on frequency, duration and severity of migraine attacks	Migraine (International Headache Society)	>1 (from inclusion criteria)	Not reported	Mean attack frequency: 4.02 (per month)
Kangasniemi, 1983[75] Sample 29 86.2% women	1) To compare the relative efficacy of propranolol and femoxetine in migraine prophylaxis, and 2) to assess the usefulness of steady state VEP (visual evoked potential) recording in the evaluation of drug effects on migraine.	Common and classic migraine	17	37	Mean frequency of migraine attacks: 7.18
Domingues, 2009[73] Sample 76 % women Not reported	To evaluate the short term efficacy and safety of the combination of low doses of propranolol and nortiptyline compared to these drugs alone	International Headache Society	Not reported	Not reported	Not reported
Carroll, 1990[173] Sample 55 69% women	To compare the efficacy and tolerability of two long-acting formulations of propranolol	Classical or common migraine (Ad hoc committee classification of headache)	Median: 14	Mean: 39	Mean frequency of migraine (month): 6.1
Kaniecki, 1997[66] Sample 37 81% women	To compare the efficacy of divalproex fodium (Depakote) with that of	Migraine without aura as defined by the International Headache	Not reported	Not reported	Mean attacks (month): 4.38

Appendix Table 82. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
	propranolol hydrochiloride (and placebo) for the prophylaxis of migraine without aura	Society			
Ziegler, 1987[74] Sample 54 73% women	To compare efficacy of propranolol and amitriptyline in the prophylaxis of migraine headache	Patients were admitted to the study when two senior neurologists agreed on the diagnosis of migraine based on the frequent occurrence of the following factors: 1) unilateral nature of the headache; 2) nausea and/or vomiting, 3) premonitory visual phenomena, and 4) headache with no consistent association with transient stress or anxiety	Not reported	Mean: 38	More than half of the headache episodes were classified as either "severe" (defined as "able to carry on some activities with discomfort but not with normal efficiency") or "disabling" (defined as "cannot carry on any normal activity, must go to bed")
Kaushik, 2005[174] Sample 192 69% women	To evaluate utility of biofeedback assisted diaphragmatic breathing and systematic relaxation in migraine and to compare their efficacy with propranolol in long term prophylaxis of migraine	International Headache Society	Not reported	Not applicable	Frequency of migraine episodes (per month): 4-5 (propranolol grp vs. biofeedback grp, 71.9% and 76%, respectively)
Kangasniemi, 1984[69] Sample 36 89% women	To compare the well-established migraine prophylactic effect of the non-selective beta-blocker propranolol with that of the beta1-selective beta-blocker metoprolol	World Federation of Neurology Research Group on Migraine and Headache, 1969	15.6	Mean: 33.8	Number of migraine attacks per 4 weeks: 5.3
Tfelt-Hansen, 1984[58] Sample 96 74% women	To compare the beta-adrenergic blocker timolol to an established drug,	Between 2 and 6 common migraine attacks per month as defined by the	20.9	Mean: 39.5	Number of migraine attacks per 4 weeks: 5.7

Appendix Table 82. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
	propranolol, and to placebo for prophylactic effect in common migraine	ad hoc committee and by Olsen			
Olerud, 1986[68] Sample 28 % women 79	To compare the prophylactic efficacy of nadolol with that of propranolol in patients with classic or common migraine	Classic and/or common migraine headaches as set forth by the Ad Hoc Committee on the Classification of Headache	Range: 2-45	Not reported (range: 17-61)	Median number of migraine attack per month during single blind placebo period: 5.6 (Nadolol), 3.6 (Propranolol)
Mathew, 1981[102] Sample 715 94.5% women	To determine propranolol's long-term effectiveness and tolerance, and to the patient's migraine status after termination of therapy	Not reported	Not reported	Mean: 38	Not reported
Albers, 1989[72] Sample 40 89.5% women	To compare the effectiveness of nifedipine to that of propranolol in the initial prophylaxis of migraine headache	Ad Hoc Committee on the Classification of Headache	Not reported	Mean: 35.2	5.2
Andersson, 1981[175] Sample 49 69.4% women	To compare the prophylactic effect of femoxetine with the effect of propranolol (Frekven) in a double-blind crossover study	Migraine was defined as paroxysmal headache associated with discomfort, possibly with inability to work, and one or more of the following symptoms: nausea, vomiting, visual disturbances and paraesthesia.	Not reported	Mean: 38	Migraine attacks per 4 weeks: 5.7
Kass, 1980[67] Sample 23 69.6% women	To compare the prophylactic effect on migraine of propronolol and clonidine	World Federation of Neurology, 1969	Not reported	Mean: 39.7	Not reported
Havanka-Kanniainen, 1988[176] Sample Not reported 81% women	To compare the efficacy and side-effects of LA propranolol 80 mg once a day with that of LA propranolol 160 mg once daily in the prophylactic	Ad Hoc Committee on the Classification of Headache	17.5	Mean: 37.7	Migraine attack: 5.1

Appendix Table 82. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
	treatment of classioc and common migraine				
Olerud, 1986[68] Sample 42 % women Not reported	To evaluate the effectiveness of a Beta-blocker (propranolol) alone, a calcium antagonist (cinnarizine) alone, and both in combination	Not reported	Not reported	Not reported	Not reported
Solomon, 1986[177] Sample Not reported % women Not reported	To compare the prophylactic antimigraine effect of the calcium entry blocker verapamil with betablocker propranolol	Not reported	Not reported	Not reported	Not reported
Ryan, 1984[178] Sample 48 73% women	To compare the relative efficacy and safety of propranolol and nadolol in the prophylactic phase of the treatment of migraine	Common or classical migraine (no definition provided)	Not reported	Not reported	Headache frequency/4 weeks: 6.3
Gerber, 1991[70] Sample 58 81% women	To ascertain, on the basis of single case statistics and time-series analysis, responder and non-responder rates for metoprolol, propranolol and nifedipine in migraine prophylaxis. In addition, an attempt was made to identify the dose relationship for the various drugs on headache parameters.	Common or classical migraine (no definition provided)	21	Mean: 42.4	Headache frequency/4 weeks: 3.55
Sudilovsky, 1987[71] Sample 140 76% women	To compare the effects of nadolol with those of propranolol in the prophylactic treatment of migraine	Classic or common migraine as defined by Ad Hoc Committee on Classification of Headahce	20.7	Mean: 39.3	Headache frequency/4 weeks (during last year): 5.29
Stensrud, 1980[60] Sample 35	To compare the effectiveness of a selective	Ad Hoc Committee on Classification of	Not reported	Not reported	Not reported

Appendix Table 82. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total sample size as randomized % women	Aim	Definition of migraine	Duration of migraine, years	Age of subjects	Baseline severity
68.6% women	and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Headache (1962)			
Olsson, 1984[179] Sample 56 73.2% women	To investigate the prophylactic effect of metopronolol under double-blind controlled conditions and to compare the effect with that of propranolol in dosages that could be regarded as starting dosage	Classical or common migraine (defined by the World Federation of Neurology Research Group on Migraine and Headache, 1969/18/)	20.7	Mean: 39.6	Migraine attack (median) / 4 weeks (during placebo run in): 5.4
Ahuja, 1985[54] Sample 26 46.2% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
Sargent, 1985[53] Sample 149 79% women	To evaluate the prophylactic effect and tolerance of naproxen sodium compared to propranolol hydrochloride and placebo in migraine	Common or classical migraine, or a combination migraine and muscle contraction headache (no definition provided)	20	Mean: 30	Not reported
Standnes, 1982[59] Sample 25 80% women	To evaluate the prophylactic effect of timolol in migraine	Common migraine attacks (as defined by the Ad Hoc Committee)	Not reported	Mean: 41.4	Mean number of attacks (4 weeks): 6.65
Diener, 2004[42] Sample 575 79.8% women	To evaluate the efficacy and safety of two doses of topiramate and safety of two doses of topiramate vs. placebo for migraine prophylaxis, with propranolol (PROP) as an active control	International Headache Society	Not reported	Median: 41	Mean monthly migraine frequency: 5.1

Appendix Table D83. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
Ashtari, 2008[168]	Not reported	Yes	Yes	Not reported	Not reported
Behan, 1980[172]	Other	Not reported	Not reported	Not reported	Not reported
Rafieian-Kopaei, 2005[62]	Other	Not reported	Yes	Not reported	All authors are from the University that sponsored the study
Kangasniemi, 1983[75]	Not reported	Not reported	Not reported	Not reported	Not reported
Domingues, 2009[73]	Not reported	Yes	Yes	Not reported	Not reported
Diener, 2002[180]	Industry	Yes	Yes	Not reported	Not reported
Carroll, 1990[173]	Not reported	Yes	Yes	Unclear	One of author is employed by industry (ICI pharmaceuticals), but unclear their relationship (no funding source reported.)
Kaniecki, 1997[66]	Industry	Not reported	Yes	Not reported	Not reported
Ziegler, 1987[74]	Grant	Not reported	Not reported	Not reported	Not reported
Kaushik, 2005[174]	Other	Yes	Yes	Not reported	Not reported
Kangasniemi, 1984[69]	Not reported	Not reported	Yes	Not reported	Not reported
Tfelt-Hansen, 1984[58]	Not reported	Not reported	Yes	Not reported	Not reported
Olerud, 1986[68]	Not reported	Not reported	Yes	Not reported	Not reported
Mathew, 1981[102]	Not reported	Not reported	Not reported	Not reported	Not reported
Albers, 1989[72]	Industry + Grant	Not reported	Yes	No	Not reported
Andersson, 1981[175]	Not reported	Not reported	Not reported	Not reported	Not reported
Kass, 1980[67]	Industry	Not reported	Not reported	Not reported	Not reported
Havanka-Kanniainen, 1988[176]	Industry	Yes	Not reported	Not reported	Not reported
Olerud, 1986[68]	Not reported	Not reported	Not reported	Not reported	Not reported
Solomon, 1986[177]	Not reported	Not reported	Not reported	Not reported	Not reported
Ryan, 1984[178]	Not reported	Not reported	Yes	Not reported	Not reported
Gerber, 1991[70]	Not reported	Not reported	Not reported	Not reported	Not reported
Sudilovsky, 1987[71]	Not reported	Yes	Yes	Not reported	Not reported
Stensrud, 1980[60]	Not reported	Not reported	Not reported	Not reported	Not reported
Olsson, 1984[179]	Not reported	Yes	Yes	Not reported	Not reported
Ahuja, 1985[54]	Industry (Inderal brand of propranolol and identical looking placebo tablets were supplied by Alkali and Chemical Corp. India Ltd.	Not reported	Not reported	Not reported	Not reported
Sargent, 1985[53]	Not reported	Not reported	Not reported	Not reported	Not reported
Standnes, 1982[59]	Industry	Not reported	Yes	Not reported	Not reported
Diener, 2004[42]	Industry	Yes	Yes	Yes	Hans-Christoph Diener has received grant/research

Appendix Table 83. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults (continued)

Reference	Funding	Ethical approval	Consent	Conflict of interest	Disclosed relationships
					support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from 3M Medica, Allergan, Almirall Prodesfarma, AstraZeneca, Bayer Vital, Böhringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, La Roche, Lilly, Novartis, MSD, Parke-Davis, Pfizer, Pharmacia, Pierre Fabre, Schaper and Brümmer, and Weber & Weber. Peer Tfelt-Hansen has been a consultant/scientific advisor for, and/or has received honoraria for oral presentation from Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, MSD, Pfizer, and Quintiles. Carl Dahlöf has been a consultant/scientific advisor for, and has received honoraria for oral presentations from Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Jansen-Cilag, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Pharmacia, and Pierre Fabre. Miguel JA Láinez has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Almirall Prodesfarma,AstraZeneca, Böhringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, MSD, Novartis, Pfizer, Pierre Fabre, and Sanofi-Synthelabo. Giorgio Sandrini has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Allergan, AstraZeneca, Bayer, Bristol- Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, Lilly,MSD, Pfizer, Pharmacia, and Solvay Pharma. Shuu-Jiun Wang has received grant/research support from and/or received honoraria for oral presentations from AstraZeneca, Glaxo- SmithKline, Johnson & Johnson, Lilly,MSD, and Pfizer. Walter Neto, Ujjwalla Vijapurkar, Aiden Doyle, and David Jacobs are employed by Johnson & Johnson Pharmaceutical Research and Development, LLC.

Appendix Table D84. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults

Reference	Masking treatment status	Planned intention to treat	Allocation concealment	Adequacy of randomization	Baseline similarity in migraine	Selective outcome reporting	Risk of bias
Ashtari, 2008[168]	Double blind	No	Unclear	Yes	F & S	Unclear	Moderate
Behan, 1980[172]	Double blind	No	Unclear	Not reported	D	Unclear	Moderate
Rafieian-Kopaei, 2005[62]	Double blind	No	Unclear	Not reported	F	Unclear	Moderate
Kangasniemi, 1983[75]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Domingues, 2009[73]	Double blind	No	Unclear	Yes	Not reported	Unclear	Moderate
Diener, 2002[180]	Double blind	Yes	Unclear	Yes	F	Unclear	Low
Carroll, 1990[173]	Double blind	No	Unclear	Not reported	F & S	Unclear	Moderate
Kaniecki, 1997[66]	Single blind	No	Unclear	Not reported	Not reported	Unclear	High
Ziegler, 1987[74]	Double blind	No	Unclear	Not reported	S	Unclear	Moderate
Kaushik, 2005[174]	Single blind	Yes	Adequate	Yes	F & S	Unclear	Moderate
Kangasniemi, 1984[69]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Tfelt-Hansen, 1984[58]	Double blind	No	Unclear	Yes	F, S & D	Unclear	Moderate
Olerud, 1986[68]	Double blind	No	Unclear	Not reported	F	Unclear	Moderate
Mathew, 1981[102]	Open-label	No	Unclear	Yes	Not reported	Unclear	High
Albers, 1989[72]	Open-label	No	Unclear	Not reported	F	Unclear	High
Andersson, 1981[175]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Kass, 1980[67]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Havanka-Kanniainen, 1988[176]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Olerud, 1986[68]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Low
Solomon, 1986[177]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Ryan, 1984[178]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Gerber, 1991[70]	Double blind	No	Unclear	Yes	F & D	Unclear	Moderate
Sudilovsky, 1987[71]	Double blind	No	Unclear	Yes	F & D	Unclear	Moderate
Stensrud, 1980[60]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Olsson, 1984[179]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Ahuja, 1985[54]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Low
Sargent, 1985[53]	Double blind	No	Unclear	Yes	Not reported	Unclear	Moderate
Standnes, 1982[59]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Diener, 2004[42]	Double blind	Yes	Unclear	Yes	F	Unclear	Low

F - migraine frequency; S - migraine severity; D - migraine duration

Appendix Table D85. Randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference Aim	Total sample [number analyzed] % females in sample	Definition of migraine	Duration of migraine	Presence of aura	Migraine frequency at baseline/month	Age of subjects (mean or median)
Louis, 1985[181] To compare the effect of clonidine with that of the β1-selective β-adrenoceptor antagonist metoprolol in patients with classical and common migraine.	33 [31] 80.6	World Federation of Neurology Research Group on Migraine and Headache, 1969	18.7 years	Not reported	3 to 10 (inclusion criterion)	Mean 35.5 years
Langohr, 1985[182] To compare the efficacy of clomipramine, a serotonin-reuptake inhibitor, as anti-migraine drug, with that of metoprolol, a beta-blocking agent	63 [34] 66.7	Ad Hoc Committee on classification of headache	20.8 years	Since 13 patients had classical migraine it was assumed that these patients had migraine with aura	Not reported	Mean 44.4 years
Grotemeyer, 1990[183] To compare in a double-blind cross-over study with a well-demarcated run-in period the effectiveness of ASA with that of a well-established beta-blocker	28 [Not reported] 82.1	Ad hoc Committee	10 years	None of the patients had aura	4 to 8	Mean 31 years
Worz, 1991[184] To compare the efficacy and safety of bisoprolol (5-10mg once daily) in migriane prophylaxis with that of the beta1-selective blocker metoprolol (50-100mg twice daily), a well established migraine prophylact drug	78 [Variable] 80.8	International Headache Society criteria	At least 2 years	55 had migraine without aura and 23 had migraine with aura	4	Not reported
Worz, 1992[185] To compare bisoprolol	125 [78] 77.6	International Headache Society	19.5 years	Migraine with aura: 27.2% and migraine	4.01	Mean 38.5 years

Appendix Table 85. Randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total sample [number analyzed] % females in sample	Definition of migraine	Duration of migraine	Presence of aura	Migraine frequency at baseline/month	Age of subjects (mean or median)
5mg once daily with metoprolol 50mg twice daily in migraine prophylaxis		criteria (Olesen, 1988)		without aura:72.8%		
Diener, 2001[186] To show equivalence of acetylsalicyclic acid with metoprolol with respect to efficacy, defined as a 50% reduction in the rate of migraine attacks.	270 [270] 81.1	International Headache Society criteria	13.8 years	50 Patients had migraine with aura	3.5	Mean 41.25 years
Schellenberg, 2008[187] To evaluate the efficacy of oral treatment with nebivolol and metoprolol in the prophylaxis of migraine attacks.	30 [30] 86.7	ICHD-II: 1.1 and 1.2	17 years	Headache with aura/other symptoms: n (%): Metoprolol: 14 (100), Nebivolol: 15 (94)	3.4	Mean 39 years

Appendix Table D86. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Disclosed relationships
Louis, 1985[181]	Not reported	Yes	Yes	Not reported	Not applicable
Langohr, 1985[182]	Industry	Not reported	Not reported	Not reported	Not applicable
Grotemeyer, 1990[183]	Not reported	Not reported	Not reported	Not reported	Not applicable
Worz, 1991[184]	Not reported	Not reported	Not reported	Not reported	Not applicable
Worz, 1992[185]	Not reported	Yes	Yes	Not reported	Not applicable
Diener, 2001[186]	Industry	Yes	Yes	Yes	G.Latta is from Bayer, Leverkusen, Germany
Schellenberg, 2008[187]	Industry	Yes	Yes	None	Not applicable

Appendix Table D87. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Baseline similarity	Selective outcome reporting	Risk of bias
Louis, 1985[181]	Double-blind	No	Unclear	Not reported	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Moderate
Langohr, 1985[182]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Moderate
Grotemeyer, 1990[183]	Double-blind	No	Unclear	Not reported	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Moderate
Worz, 1991[184]	Double-blind	No	Unclear	Not reported	Frequency: similar; Severity: not reported; Duration: not reported	Unclear	Moderate
Worz, 1992[185]	Double-blind	No	Unclear	Not reported	Frequency: similar: Severity: not reported: Duration: not reported	Unclear	Moderate
Diener, 2001[186]	Double-blind	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Low
Schellenberg, 2008[187]	Double-blind	Yes	Unclear	No, there were no males in the metoprolol group	Frequency: similar; Severity: similar; Duration: similar	Unclear	Moderate

Appendix Table D88. Strength of evidence of comparative effectiveness of beta-blockers for migraine prevention in adults

Definition of the outcome	Reference	Active drug	Control drug	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Reduction of frequency of attacks by more than 50%	Worz, 1992[185]	Metoprolol	Bisoprolol	Moderate	Yes	Not applicable	No	Low
Responder rate(at least 50% in number of attacks from baseline to endpoint)	Schellenberg, 2008[187]	Metoprolol	Nebivolol	Moderate	Yes	Not applicable	No	Low
Reduction of attacks more than 50%	Grotemeyer, 1990[183]	Metoprolol	Acetylsalicylic acid	Moderate	Yes	Not applicable	Yes	Low
Responder rate (Reduction in the number of migraine attacks greater than 50%)	Diener, 2001[186]	Metoprolol	Acetylsalicylic acid, 1500mg/day	Low	Yes	Not applicable	No	Low
Reduction of more than 50% in the number of migraine days	Louis, 1985[181]	Metoprolol	Clonidine	Moderate	Yes	Not applicable	No	Low

Appendix Table D89. Comparative effectiveness of beta-blockers on migraine frequency, severity, and impact (results from randomized controlled clinical trials)

Definition of the outcome	Reference Risk of bias	Active drug Dose	Control drug, Dose	Randomized to active/control drug	Mean [standard deviation] with active drug	Mean [standard deviation] with control drug	Mean difference (95% CI)
Number of attacks per 4 weeks	Worz, 1991[184] Moderate	Bisoprolol 5 to 10mg once daily	Metoprolol 50 to 100mg twice daily	78/78	Not reported	Not reported	0.1 (-0.2 to 0.4)
Mean frequency per 28 days in phase I	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	65/60	2.0 [1.7]	2.4 [2.0]	-0.4 (-1.0 to 0.3)
Mean frequency per 28 days in phase II	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	60/65	2.0 [1.7]	1.8 [1.7]	0.2 (-0.4 to 0.8)
Mean frequency per 28 days (overall)	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	125/125	2.0 [1.5]	2.1 [1.8]	-0.1 (-0.5 to 0.4)
Frequency of migraine attacks	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	1.3 [1.0]	1.6 [1.5]	-0.3 (-1.2 to 0.6)
Duration of migraine attacks at endpoint (hours)	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	26.0 [55.0]	15.0 [14.0]	11.0 (-18.6 to 40.6)
Severity at endpoint (measured on 100 mm visual analog scale)	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	54.0 [16.0]	50.0 [24.0]	4.0 (-10.4 to 18.4)
MIDAS: days with headache	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	13.0 [18.0]	14.0 [14.0]	-1.0 (-12.7 to 10.7)
MIDAS: pain intensity	Schellenberg, 2008[187]	Metoprolol Week 1: 47.5mg,	Nebivolol 5mg daily	14/16	6.0 [2.0]	6.0 [3.0]	0.0 (-1.8 to 1.8)

Appendix Table 89. Comparative effectiveness of beta-blockers on migraine frequency, severity, and impact (results from randomized controlled clinical trials)

Definition of the outcome	Reference Risk of bias	Active drug Dose	Control drug, Dose	Randomized to active/control drug	Mean [standard deviation] with active drug	Mean [standard deviation] with control drug	Mean difference (95% CI)
	Moderate	week 2: 95mg, week 3 - 16:142.5mg					
Quality of life(SF-36): Physical	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	46.0 [7.0]	50.0 [10.0]	-4.0 (-10.1 to 2.1)
Quality of life(SF-36): Mental	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	48.0 [8.0]	45.0 [13.0]	3.0 (-4.6 to 10.6)
% change in frequency of migraine attacks	**Grotemeyer, 1990[183] Moderate**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 1500mg/day (**	**28/28**	**-50.0 [18.0]**	**-26.0 [22.0]**	**-24.0 (-34.5 to -13.5)**
Intensity of attacks	Grotemeyer, 1990[183] Moderate	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 1500mg/day (	28/28	1.6 [0.7]	1.4 [0.5]	0.2 (-0.1 to 0.5)
Frequency of migraine attacks	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 300mg/day**	**135/135**	**1.8 [1.6]**	**2.4 [1.9]**	**-0.5 (-1.0 to -0.1)**

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D90. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials)

Definition of the outcome	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group]	Events/ randomized [rate of outcome in control group]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Reduction of frequency of attacks by more than 50%	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	11/125 [8.8]	12/125 [9.6]	0.9 (0.4 to 2.0)	-0.01 (-0.08 to 0.06)
Patients rated treatment as more effective	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	28/125 [22.4]	37/125 [29.6]	0.8 (0.5 to 1.2)	-0.07 (-0.18 to 0.04)
MIDAS :No impairment	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	2/16 [12.5]	1.1 (0.2 to 7.1)	0.02 (-0.23 to 0.26)
MIDAS :Severe impairment	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	5/16 [31.3]	0.5 (0.1 to 2.0)	-0.17 (-0.46 to 0.12)
MIDAS :Moderate impairment	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	4/14 [28.6]	6/16 [37.5]	0.8 (0.3 to 2.2)	-0.09 (-0.42 to 0.25)
MIDAS :Mild impairment	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	5/14 [35.7]	2/16 [12.5]	2.9 (0.7 to 12.5)	0.23 (-0.07 to 0.53)
Responder rate(at least 50% in number of attacks from baseline to endpoint)	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	8/14 [57.0]	8/16 [50.0]	1.1 (0.6 to 2.2)	0.07 (-0.29 to 0.43)

Appendix Table 90. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition of the outcome	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group]	Events/ randomized [rate of outcome in control group]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Patients using pain medications at endpoint	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	10/14 [71.4]	10/16 [62.5]	1.1 (0.7 to 1.9)	0.09 (-0.25 to 0.42)
Pain intensity: mild	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	6/135 [4.4]	9/135 [6.7]	0.7 (0.2 to 1.8)	-0.02 (-0.08 to 0.03)
Reduction of attacks more than 50%	**Grotemeyer, 1990[183] Moderate**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 1500mg/day (**	**14/28 [50.0]**	**3/28 [10.7]**	**4.7 (1.5 to 14.5)**	**0.39 (0.18 to 0.61)**
Photophobia: mild	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	17/135 [12.6]	23/135 [17.0]	0.7 (0.4 to 1.3)	-0.04 (-0.13 to 0.04)
Phonophobia: mild	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	25/135 [18.5]	17/135 [12.6]	1.5 (0.8 to 2.6)	0.06 (-0.03 to 0.15)
Nausea: mild	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	33/135 [24.4]	22/135 [16.3]	1.5 (0.9 to 2.4)	0.08 (-0.01 to 0.18)

Appendix Table 90. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition of the outcome	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group]	Events/ randomized [rate of outcome in control group]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Vomiting: mild	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	38/135 [28.1]	32/135 [23.7]	1.2 (0.8 to 1.8)	0.04 (-0.06 to 0.15)
Responder rate (Reduction in the number of migraine attacks greater than 50%)	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 300mg/day**	**40/135 [29.6]**	**61/135 [45.2]**	**0.7 (0.5 to 0.9)**	**-0.16 (-0.27 to -0.04)**
Reduction of more than 50% in the number of migraine days	Louis, 1985[181] Moderate	Metoprolol 50mg BID	Clonidine 50µg BID	10/31 [32.3]	8/31 [25.8]	1.3 (0.6 to 2.7)	0.06 (-0.16 to 0.29)
Migraine days with nausea symptoms	Louis, 1985[181] Moderate	Metoprolol 50mg BID	Clonidine 50µg BID	11/31 [35.0]	12/31 [39.0]	0.9 (0.5 to 1.8)	-0.03 (-0.27 to 0.21)
Migraine attacks accompanied by visual disturbances	Louis, 1985[181] Moderate	Metoprolol 50mg BID	Clonidine 50µg BID	12/31 [38.7]	17/31 [54.8]	0.7 (0.4 to 1.2)	-0.16 (-0.41 to 0.08)
Subjective therapeutic evaluation: Marked or moderate	Louis, 1985[181] Moderate	Metoprolol 50mg BID	Clonidine 50µg BID	22/31 [71.0]	15/31 [48.4]	1.5 (1.0 to 2.2)	0.23 (-0.01 to 0.46)
Number of migraine days reduced	**Louis, 1985[181] Moderate**	**Metoprolol 50mg BID**	**Clonidine 50µg BID**	**24/31 [77.4]**	**14/31 [45.2]**	**1.7 (1.1 to 2.6)**	**0.32 (0.09 to 0.55)**

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D91. Net-work Bayesian Meta-analysis of clinically important (>50%) reduction in migraine with preventive drugs in adults, results from randomized controlled clinical trials

Control / Active	Placebo	Topiramate	Valproate or divalproex	Propranolol	ACE inhibitors or angiotensin blockers	Off label beta-blockers	Antidepressants	Off label anti epileptics	Ergot alkaloids
Topiramate	**2.9 (1.9;4.5)**		0.9 (0.4;1.9)	0.8 (0.5;1.5)	**0.2 (0.0;0.5)**	0.6 (0.3;1.2)	1.0 (0.5;2.0)	1.3 (0.6;2.6)	2.4 (0.5;11.7)
Valproate or divalproex	**3.4 (1.7;7.0)**	1.2 (0.5;2.6)		1.0 (0.4;2.1)	**0.2 (0.0;0.7)**	0.7 (0.3;1.6)	1.2 (0.5;3.0)	1.5 (0.6;3.8)	2.7 (0.5;14.8)
Propranolol	**3.5 (2.2;5.8)**	1.2 (0.7;2.2)	1.0 (0.5;2.2)		**0.2 (0.1;0.6)**	0.7 (0.4;1.3)	1.2 (0.6;2.4)	1.5 (0.7;3.4)	2.9 (0.6;14.7)
ACE inhibitors or Angiotensin blockers	**17.3 (6.2;58.9)**	**6.0 (2.0;21.4)**	**5.2 (1.5;20.9)**	**4.9 (1.6;17.5)**		**3.6 (1.1;13.2)**	**6.0 (1.8;23.6)**	**7.7 (2.3;28.8)**	**14.3 (2.3;100.5)**
Off label beta-blockers	**4.8 (2.9;8.3)**	1.7 (0.9;3.2)	1.4 (0.6;3.3)	1.4 (0.8;2.4)	**0.3 (0.1;0.9)**		1.7 (0.8;3.7)	2.1 (0.9;4.8)	3.9 (0.8;19.9)
Antidepressants	**2.9 (1.5;5.6)**	1.0 (0.5;2.0)	0.8 (0.3;2.1)	0.8 (0.4;1.6)	**0.2 (0.0;0.6)**	0.6 (0.3;1.3)		1.3 (0.5;3.1)	2.3 (0.5;12.6)
Off label anti epileptics	**2.3 (1.2;4.4)**	0.8 (0.4;1.6)	0.7 (0.3;1.8)	0.6 (0.3;1.4)	**0.1 (0.0;0.4)**	0.5 (0.2;1.1)	0.8 (0.3;1.9)		1.9 (0.4;9.9)
Ergot alkaloids	1.2 (0.3;5.7)	0.4 (0.1;2.1)	0.4 (0.1;2.0)	0.3 (0.1;1.7)	**0.1 (0.0;0.4)**	0.3 (0.1;1.3)	0.4 (0.1;2.2)	0.5 (0.1;2.9)	

Appendix Table D92. Net-work Bayesian Meta-analysis of clinically important (>50%) reduction in migraine with preventive drugs in adults, results from randomized controlled clinical trials (separate analysis for off label beta-blockers)

Control / Active	Propranolol	Timolol	Metoprolol	Other beta-blockers	Antidepressants	Anti-epileptics	ACE inhibitors or angiotensin blockers
Propranolol		**0.3 (0.0;0.9)**	**0.4 (0.0;0.8)**	**0.2 (0.0;0.5)**	0.6 (0.0;1.2)	0.7 (0.0;1.2)	**0.1 (0.0;0.2)**
Timolol	0.4 (0.0;1.1)		**0.3 (0.0;0.8)**	**0.1 (0.0;0.5)**	0.4 (0.0;1.4)	0.5 (0.0;1.4)	**0.1 (0.0;0.3)**
Metoprolol	0.6 (0.0;1.3)	0.4 (0.0;1.2)		**0.2 (0.0;0.6)**	0.6 (0.0;1.6)	0.8 (0.0;1.6)	**0.1 (0.0;0.3)**
Other Beta-blockers	0.9 (0.0;2.2)	0.5 (0.0;2.0)	0.6 (0.0;1.6)		0.9 (0.0;2.6)	1.0 (0.0;2.7)	**0.1 (0.0;0.5)**
Antidepressants	**0.4 (0.0;0.8)**	**0.2 (0.0;0.7)**	**0.2 (0.0;0.6)**	**0.1 (0.0;0.4)**		0.5 (0.0;1.0)	**0.0 (0.0;0.2)**
Anti-epileptics	**0.4 (0.0;0.8)**	**0.3 (0.0;0.7)**	**0.3 (0.0;0.6)**	**0.1 (0.0;0.4)**	0.5 (0.0;1.0)		**0.1 (0.0;0.2)**
ACE inhibitors or angiotensin blockers	1.2 (0.1;4.1)	0.9 (0.1;3.7)	0.8 (0.1;3.2)	**0.4 (0.0;1.9)**	1.3 (0.1;5.1)	1.6 (0.1;5.1)	

Appendix Table D93. Net-work Bayesian Meta-analysis of clinically important (>50%) reduction in migraine with preventive drugs in adults, results from randomized controlled clinical trials (adding NSAD, all drug classes)

Control / Active	Placebo	Topiramate	Dival-proex	Pro-pranolol	Angi-otensin Inhibiting drugs	Calcium channel antago-nists	Beta-blockers	Anti-depressants	Anti-epileptics	Ergot alkaloids	NSAD	Anti-adrenergics
Topiramate	**3.2 (2.1; 5.1)**		0.9 (0.4; 2.0)	0.9 (0.5; 1.6)	**0.2 (0.1; 0.7)**	0.9 (0.5; 1.7)	0.6 (0.3; 1.3)	1.0 (0.5; 2.0)	1.4 (0.7; 2.8)	2.6 (0.5; 12.1)	0.8 (0.3; 2.0)	0.7 (0.3; 1.6)
Divalproex	**3.5 (1.8; 7.3)**	1.1 (0.5; 2.4)		1.0 (0.5; 2.1)	**0.3 (0.1; 0.9)**	1.0 (0.5; 2.2)	0.7 (0.3; 1.6)	1.1 (0.5; 2.8)	1.5 (0.6; 3.8)	2.8 (0.5; 14.9)	0.9 (0.3; 2.5)	0.8 (0.3; 1.9)
Propranolol	**3.6 (2.3; 5.8)**	1.1 (0.6; 2.0)	1.0 (0.5; 2.2)		**0.3 (0.1; 0.8)**	1.0 (0.6; 1.7)	0.7 (0.4; 1.3)	1.2 (0.6; 2.2)	1.6 (0.8; 3.3)	2.9 (0.6; 13.8)	0.9 (0.4; 2.2)	0.8 (0.4; 1.7)
Angiotensin inhibiting drugs	**13.5 (4.7; 44.8)**	**4.2 (1.4; 14.9)**	**3.9 (1.1; 14.8)**	**3.8 (1.2; 13.4)**		**3.9 (1.2; 13.6)**	2.8 (0.9; 9.9)	**4.3 (1.3; 16.0)**	**5.9 (1.8; 22.0)**	**10.8 (1.8; 74.2)**	**3.5 (1.0; 15.1)**	3.1 (0.9; 12.1)
Calcium channel antagonists	**3.5 (2.2; 5.8)**	1.1 (0.6; 2.0)	1.0 (0.5; 2.2)	1.0 (0.6; 1.6)	**0.3 (0.1; 0.8)**		0.7 (0.4; 1.3)	1.1 (0.6; 2.3)	1.5 (0.7; 3.3)	2.8 (0.6; 13.6)	0.9 (0.4; 2.2)	0.8 (0.4; 1.6)
Beta-blockers	**4.9 (2.9; 8.6)**	1.5 (0.8; 3.0)	1.4 (0.6; 3.3)	1.4 (0.8; 2.4)	0.4 (0.1; 1.2)	1.4 (0.8; 2.6)		1.6 (0.7; 3.4)	2.2 (1.0; 4.9)	3.9 (0.9; 19.6)	1.3 (0.6; 2.9)	1.1 (0.5; 2.4)
Anti-depressants	**3.1 (1.7; 5.8)**	1.0 (0.5; 1.9)	0.9 (0.4; 2.1)	0.9 (0.4; 1.7)	**0.2 (0.1; 0.8)**	0.9 (0.4; 1.8)	0.6 (0.3; 1.3)		1.4 (0.6; 3.1)	2.5 (0.5; 12.8)	0.8 (0.3; 2.2)	0.7 (0.3; 1.7)
Antiepileptics	**2.3 (1.3; 4.1)**	0.7 (0.4; 1.4)	0.7 (0.3; 1.6)	0.6 (0.3; 1.3)	**0.2 (0.0; 0.5)**	0.7 (0.3; 1.4)	0.5 (0.2; 1.0)	0.7 (0.3; 1.6)		1.8 (0.4; 9.2)	0.6 (0.2; 1.6)	0.5 (0.2; 1.3)
Ergot alkaloids	1.2 (0.3; 5.5)	0.4 (0.1; 1.9)	0.4 (0.1; 1.8)	0.3 (0.1; 1.6)	**0.1 (0.0; 0.6)**	0.4 (0.1; 1.6)	0.3 (0.1; 1.2)	0.4 (0.1; 1.9)	0.5 (0.1; 2.6)		0.3 (0.1; 1.7)	0.3 (0.1; 1.4)
NSAD	**3.8 (1.8; 8.2)**	1.2 (0.5; 2.9)	1.1 (0.4; 3.1)	1.1 (0.5; 2.5)	0.3 (0.1; 1.0)	1.1 (0.4; 2.6)	0.8 (0.3; 1.7)	1.2 (0.5; 3.2)	1.7 (0.6; 4.3)	3.1 (0.6; 15.7)		0.9 (0.3; 2.3)
Anti-adrenergics	**4.3 (2.2; 9.2)**	1.4 (0.6; 3.0)	1.2 (0.5; 3.0)	1.2 (0.6; 2.5)	0.3 (0.1; 1.1)	1.2 (0.6; 2.5)	0.9 (0.4; 1.9)	1.4 (0.6; 3.4)	1.9 (0.8; 4.8)	3.5 (0.7; 18.9)	1.1 (0.4; 3.3)	

Appendix Table D94. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo)

Active	Control	Odds ratio vs. placebo with active drug	Lower 95% CI	Upper 95% CI	Odds ratio vs. placebo with control drug	Lower 95% CI	Upper 95% CI	Odds ratio active vs. control drug	Lower 95% CI	Upper 95% CI
Amitriptyline	Atenolol	2.45	1.32	4.54	25.24	1.36	467.87	0.10	0.00	1.92
Amitriptyline	Candesartan	2.45	1.32	4.54	45.12	5.86	347.47	0.05	0.01	0.46
Amitriptyline	Captopril	2.45	1.32	4.54	47.22	2.24	996.02	0.05	0.00	1.16
Amitriptyline	Carbamazepin	2.45	1.32	4.54	10.16	3.43	30.12	0.24	0.07	0.84
Amitriptyline	Clonidine	2.45	1.32	4.54	31.24	1.73	563.16	0.08	0.00	1.51
Amitriptyline	Fenoprofen	2.45	1.32	4.54	3.17	1.11	9.05	0.77	0.23	2.61
Amitriptyline	Flurbiprofen	2.45	1.32	4.54	5.22	1.49	18.35	0.47	0.12	1.90
Amitriptyline	Gabapentin	2.45	1.32	4.54	2.44	1.29	4.59	1.00	0.41	2.43
Amitriptyline	Lisinopril	2.45	1.32	4.54	37.73	2.19	649.03	0.06	0.00	1.19
Amitriptyline	Metoprolol	2.45	1.32	4.54	2.54	1.36	4.74	0.97	0.40	2.33
Amitriptyline	Propranolol	2.45	1.32	4.54	2.93	1.96	4.39	0.83	0.40	1.75
Amitriptyline	Sodium valproate	2.45	1.32	4.54	4.03	1.40	11.61	0.61	0.18	2.07
Amitriptyline	Timolol	2.45	1.32	4.54	3.32	1.94	5.68	0.74	0.33	1.67
Amitriptyline	Tolfenamic Acid	2.45	1.32	4.54	11.94	2.42	59.03	0.21	0.04	1.14
Amitriptyline	Topiramate	2.45	1.32	4.54	2.84	1.88	4.28	0.86	0.41	1.81
Amitriptyline	Venlafaxine	2.45	1.32	4.54	29.64	1.58	555.72	0.08	0.00	1.65
Atenolol	Candesartan	25.24	1.36	467.87	45.12	5.86	347.47	0.56	0.02	19.72
Atenolol	Captopril	25.24	1.36	467.87	47.22	2.24	996.02	0.53	0.01	36.42
Atenolol	Carbamazepin	25.24	1.36	467.87	10.16	3.43	30.12	2.48	0.11	55.98
Atenolol	Clonidine	25.24	1.36	467.87	31.24	1.73	563.16	0.81	0.01	49.21
Atenolol	Fenoprofen	25.24	1.36	467.87	3.17	1.11	9.05	7.95	0.36	176.93
Atenolol	Flurbiprofen	25.24	1.36	467.87	5.22	1.49	18.35	4.83	0.20	116.00
Atenolol	Gabapentin	25.24	1.36	467.87	2.44	1.29	4.59	10.35	0.52	205.39
Atenolol	Lisinopril	25.24	1.36	467.87	37.73	2.19	649.03	0.67	0.01	39.43
Atenolol	Metoprolol	25.24	1.36	467.87	2.54	1.36	4.74	9.95	0.50	197.05
Atenolol	Propranolol	25.24	1.36	467.87	2.93	1.96	4.39	8.61	0.45	164.01
Atenolol	Sodium valproate	25.24	1.36	467.87	4.03	1.40	11.61	6.26	0.28	139.69
Atenolol	Timolol	25.24	1.36	467.87	3.32	1.94	5.68	7.61	0.39	148.14
Atenolol	Tolfenamic Acid	25.24	1.36	467.87	11.94	2.42	59.03	2.11	0.08	58.96
Atenolol	Topiramate	25.24	1.36	467.87	2.84	1.88	4.28	8.90	0.47	169.73
Atenolol	Venlafaxine	25.24	1.36	467.87	29.64	1.58	555.72	0.85	0.01	53.33
Candesartan	Captopril	45.12	5.86	347.47	47.22	2.24	996.02	0.96	0.02	37.47
Candesartan	Carbamazepin	45.12	5.86	347.47	10.16	3.43	30.12	4.44	0.44	44.83
Candesartan	Clonidine	45.12	5.86	347.47	31.24	1.73	563.16	1.44	0.04	49.76

Appendix Table 94. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (continued)

Active	Control	Odds ratio vs. placebo with active drug	Lower 95% CI	Upper 95% CI	Odds ratio vs. placebo with control drug	Lower 95% CI	Upper 95% CI	Odds ratio active vs. control drug	Lower 95% CI	Upper 95% CI
Candesartan	Fenoprofen	45.12	5.86	347.47	3.17	1.11	9.05	14.22	1.43	141.06
Candesartan	Flurbiprofen	45.12	5.86	347.47	5.22	1.49	18.35	8.64	0.79	94.90
Candesartan	Gabapentin	45.12	5.86	347.47	2.44	1.29	4.59	18.51	2.18	156.88
Candesartan	Lisinopril	45.12	5.86	347.47	37.73	2.19	649.03	1.20	0.04	39.66
Candesartan	Metoprolol	45.12	5.86	347.47	2.54	1.36	4.74	17.78	2.10	150.41
Candesartan	Propranolol	45.12	5.86	347.47	2.93	1.96	4.39	15.38	1.92	123.24
Candesartan	Sodium valproate	45.12	5.86	347.47	4.03	1.40	11.61	11.19	1.12	111.49
Candesartan	Timolol	45.12	5.86	347.47	3.32	1.94	5.68	13.60	1.65	112.30
Candesartan	Tolfenamic Acid	45.12	5.86	347.47	11.94	2.42	59.03	3.78	0.28	50.49
Candesartan	Topiramate	45.12	5.86	347.47	2.84	1.88	4.28	15.90	1.98	127.60
Candesartan	Venlafaxine	45.12	5.86	347.47	29.64	1.58	555.72	1.52	0.04	54.17
Captopril	Carbamazepin	47.22	2.24	996.02	10.16	3.43	30.12	4.65	0.18	118.24
Captopril	Clonidine	47.22	2.24	996.02	31.24	1.73	563.16	1.51	0.02	101.01
Captopril	Fenoprofen	47.22	2.24	996.02	3.17	1.11	9.05	14.88	0.59	373.92
Captopril	Flurbiprofen	47.22	2.24	996.02	5.22	1.49	18.35	9.04	0.33	244.45
Captopril	Gabapentin	47.22	2.24	996.02	2.44	1.29	4.59	19.37	0.86	436.01
Captopril	Lisinopril	47.22	2.24	996.02	37.73	2.19	649.03	1.25	0.02	81.00
Captopril	Metoprolol	47.22	2.24	996.02	2.54	1.36	4.74	18.61	0.83	418.35
Captopril	Propranolol	47.22	2.24	996.02	2.93	1.96	4.39	16.10	0.74	348.74
Captopril	Sodium valproate	47.22	2.24	996.02	4.03	1.40	11.61	11.71	0.46	295.18
Captopril	Timolol	47.22	2.24	996.02	3.32	1.94	5.68	14.24	0.64	314.72
Captopril	Tolfenamic Acid	47.22	2.24	996.02	11.94	2.42	59.03	3.95	0.13	123.61
Captopril	Topiramate	47.22	2.24	996.02	2.84	1.88	4.28	16.65	0.77	360.90
Captopril	Venlafaxine	47.22	2.24	996.02	29.64	1.58	555.72	1.59	0.02	109.41
Carbamazepin	Clonidine	10.16	3.43	30.12	31.24	1.73	563.16	0.33	0.01	7.14
Carbamazepin	Fenoprofen	10.16	3.43	30.12	3.17	1.11	9.05	3.20	0.71	14.49
Carbamazepin	Flurbiprofen	10.16	3.43	30.12	5.22	1.49	18.35	1.95	0.37	10.24
Carbamazepin	Gabapentin	10.16	3.43	30.12	2.44	1.29	4.59	4.17	1.19	14.66
Carbamazepin	Lisinopril	10.16	3.43	30.12	37.73	2.19	649.03	0.27	0.01	5.66
Carbamazepin	Metoprolol	10.16	3.43	30.12	2.54	1.36	4.74	4.01	1.14	14.03
Carbamazepin	Propranolol	10.16	3.43	30.12	2.93	1.96	4.39	3.47	1.09	11.04
Carbamazepin	Sodium valproate	10.16	3.43	30.12	4.03	1.40	11.61	2.52	0.55	11.48
Carbamazepin	Timolol	10.16	3.43	30.12	3.32	1.94	5.68	3.06	0.91	10.29
Carbamazepin	Tolfenamic Acid	10.16	3.43	30.12	11.94	2.42	59.03	0.85	0.12	5.88
Carbamazepin	Topiramate	10.16	3.43	30.12	2.84	1.88	4.28	3.58	1.12	11.44
Carbamazepin	Venlafaxine	10.16	3.43	30.12	29.64	1.58	555.72	0.34	0.02	7.81

Appendix Table 94. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (continued)

Active	Control	Odds ratio vs. placebo with active drug	Lower 95% CI	Upper 95% CI	Odds ratio vs. placebo with control drug	Lower 95% CI	Upper 95% CI	Odds ratio active vs. control drug	Lower 95% CI	Upper 95% CI
Clonidine	Fenoprofen	31.24	1.73	563.16	3.17	1.11	9.05	9.85	0.45	213.32
Clonidine	Flurbiprofen	31.24	1.73	563.16	5.22	1.49	18.35	5.98	0.26	139.94
Clonidine	Gabapentin	31.24	1.73	563.16	2.44	1.29	4.59	12.82	0.66	247.38
Clonidine	Lisinopril	31.24	1.73	563.16	37.73	2.19	649.03	0.83	0.01	47.84
Clonidine	Metoprolol	31.24	1.73	563.16	2.54	1.36	4.74	12.32	0.64	237.33
Clonidine	Propranolol	31.24	1.73	563.16	2.93	1.96	4.39	10.65	0.57	197.46
Clonidine	Sodium valproate	31.24	1.73	563.16	4.03	1.40	11.61	7.75	0.36	168.43
Clonidine	Timolol	31.24	1.73	563.16	3.32	1.94	5.68	9.42	0.50	178.39
Clonidine	Tolfenamic Acid	31.24	1.73	563.16	11.94	2.42	59.03	2.62	0.10	71.22
Clonidine	Topiramate	31.24	1.73	563.16	2.84	1.88	4.28	11.01	0.59	204.36
Clonidine	Venlafaxine	31.24	1.73	563.16	29.64	1.58	555.72	1.05	0.02	64.73
Fenoprofen	Flurbiprofen	3.17	1.11	9.05	5.22	1.49	18.35	0.61	0.12	3.12
Fenoprofen	Gabapentin	3.17	1.11	9.05	2.44	1.29	4.59	1.30	0.38	4.43
Fenoprofen	Lisinopril	3.17	1.11	9.05	37.73	2.19	649.03	0.08	0.00	1.74
Fenoprofen	Metoprolol	3.17	1.11	9.05	2.54	1.36	4.74	1.25	0.37	4.24
Fenoprofen	Propranolol	3.17	1.11	9.05	2.93	1.96	4.39	1.08	0.35	3.33
Fenoprofen	Sodium valproate	3.17	1.11	9.05	4.03	1.40	11.61	0.79	0.18	3.49
Fenoprofen	Timolol	3.17	1.11	9.05	3.32	1.94	5.68	0.96	0.29	3.11
Fenoprofen	Tolfenamic Acid	3.17	1.11	9.05	11.94	2.42	59.03	0.27	0.04	1.80
Fenoprofen	Topiramate	3.17	1.11	9.05	2.84	1.88	4.28	1.12	0.36	3.45
Fenoprofen	Venlafaxine	3.17	1.11	9.05	29.64	1.58	555.72	0.11	0.00	2.41
Flurbiprofen	Gabapentin	5.22	1.49	18.35	2.44	1.29	4.59	2.14	0.52	8.75
Flurbiprofen	Lisinopril	5.22	1.49	18.35	37.73	2.19	649.03	0.14	0.01	3.10
Flurbiprofen	Metoprolol	5.22	1.49	18.35	2.54	1.36	4.74	2.06	0.51	8.38
Flurbiprofen	Propranolol	5.22	1.49	18.35	2.93	1.96	4.39	1.78	0.48	6.66
Flurbiprofen	Sodium valproate	5.22	1.49	18.35	4.03	1.40	11.61	1.30	0.25	6.69
Flurbiprofen	Timolol	5.22	1.49	18.35	3.32	1.94	5.68	1.58	0.40	6.17
Flurbiprofen	Tolfenamic Acid	5.22	1.49	18.35	11.94	2.42	59.03	0.44	0.06	3.34
Flurbiprofen	Topiramate	5.22	1.49	18.35	2.84	1.88	4.28	1.84	0.49	6.90
Flurbiprofen	Venlafaxine	5.22	1.49	18.35	29.64	1.58	555.72	0.18	0.01	4.28
Gabapentin	Lisinopril	2.44	1.29	4.59	37.73	2.19	649.03	0.06	0.00	1.19
Gabapentin	Metoprolol	2.44	1.29	4.59	2.54	1.36	4.74	0.96	0.39	2.34
Gabapentin	Propranolol	2.44	1.29	4.59	2.93	1.96	4.39	0.83	0.39	1.76
Gabapentin	Sodium valproate	2.44	1.29	4.59	4.03	1.40	11.61	0.60	0.18	2.07
Gabapentin	Timolol	2.44	1.29	4.59	3.32	1.94	5.68	0.74	0.32	1.69
Gabapentin	Tolfenamic Acid	2.44	1.29	4.59	11.94	2.42	59.03	0.20	0.04	1.14

Appendix Table 94. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (continued)

Active	Control	Odds ratio vs. placebo with active drug	Lower 95% CI	Upper 95% CI	Odds ratio vs. placebo with control drug	Lower 95% CI	Upper 95% CI	Odds ratio active vs. control drug	Lower 95% CI	Upper 95% CI
Gabapentin	Topiramate	2.44	1.29	4.59	2.84	1.88	4.28	0.86	0.40	1.83
Gabapentin	Venlafaxine	2.44	1.29	4.59	29.64	1.58	555.72	0.08	0.00	1.65
Lisinopril	Metoprolol	37.73	2.19	649.03	2.54	1.36	4.74	14.87	0.81	273.82
Lisinopril	Propranolol	37.73	2.19	649.03	2.93	1.96	4.39	12.86	0.73	227.68
Lisinopril	Sodium valproate	37.73	2.19	649.03	4.03	1.40	11.61	9.36	0.45	194.67
Lisinopril	Timolol	37.73	2.19	649.03	3.32	1.94	5.68	11.38	0.63	205.76
Lisinopril	Tolfenamic Acid	37.73	2.19	649.03	11.94	2.42	59.03	3.16	0.12	82.56
Lisinopril	Topiramate	37.73	2.19	649.03	2.84	1.88	4.28	13.30	0.75	235.63
Lisinopril	Venlafaxine	37.73	2.19	649.03	29.64	1.58	555.72	1.27	0.02	75.65
Metoprolol	Propranolol	2.54	1.36	4.74	2.93	1.96	4.39	0.86	0.41	1.82
Metoprolol	Sodium valproate	2.54	1.36	4.74	4.03	1.40	11.61	0.63	0.18	2.15
Metoprolol	Timolol	2.54	1.36	4.74	3.32	1.94	5.68	0.76	0.34	1.74
Metoprolol	Tolfenamic Acid	2.54	1.36	4.74	11.94	2.42	59.03	0.21	0.04	1.18
Metoprolol	Topiramate	2.54	1.36	4.74	2.84	1.88	4.28	0.89	0.42	1.89
Metoprolol	Venlafaxine	2.54	1.36	4.74	29.64	1.58	555.72	0.09	0.00	1.71
Propranolol	Sodium valproate	2.93	1.96	4.39	4.03	1.40	11.61	0.73	0.23	2.26
Propranolol	Timolol	2.93	1.96	4.39	3.32	1.94	5.68	0.88	0.45	1.73
Propranolol	Tolfenamic Acid	2.93	1.96	4.39	11.94	2.42	59.03	0.25	0.05	1.28
Propranolol	Topiramate	2.93	1.96	4.39	2.84	1.88	4.28	1.03	0.58	1.84
Propranolol	Venlafaxine	2.93	1.96	4.39	29.64	1.58	555.72	0.10	0.01	1.91
Sodium valproate	Timolol	4.03	1.40	11.61	3.32	1.94	5.68	1.22	0.37	3.98
Sodium valproate	Tolfenamic Acid	4.03	1.40	11.61	11.94	2.42	59.03	0.34	0.05	2.29
Sodium valproate	Topiramate	4.03	1.40	11.61	2.84	1.88	4.28	1.42	0.46	4.42
Sodium valproate	Venlafaxine	4.03	1.40	11.61	29.64	1.58	555.72	0.14	0.01	3.07
Timolol	Tolfenamic Acid	3.32	1.94	5.68	11.94	2.42	59.03	0.28	0.05	1.50
Timolol	Topiramate	3.32	1.94	5.68	2.84	1.88	4.28	1.17	0.59	2.30
Timolol	Venlafaxine	3.32	1.94	5.68	29.64	1.58	555.72	0.11	0.01	2.20
Tolfenamic Acid	Topiramate	11.94	2.42	59.03	2.84	1.88	4.28	4.21	0.81	21.92
Tolfenamic Acid	Venlafaxine	11.94	2.42	59.03	29.64	1.58	555.72	0.40	0.01	11.35
Topiramate	Venlafaxine	2.84	1.88	4.28	29.64	1.58	555.72	0.10	0.00	1.85

Appendix Table D95. Comparative effectiveness of antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial[188]

Definition of the outcome	Active treatment	Control treatment	Events/ Randomized rate,% with active treatment	Events/ Randomized rate,% with drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
>60% reduction in HI in last 4 weeks of treatment phase	**Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)**	**Amitriptyline 100mg/day**	**17/34 22.15**	**34/77 48.65**	**0.5 (0.3 to 0.7)**	**-0.26 (-0.41 to -0.12)**
>60% reduction in HI during the 4-week post-treatment followup phase	Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)	Amitriptyline 100mg/day	17/11 22.15	11/77 15.75	1.4 (0.7 to 2.8)	0.06 (-0.06 to 0.19)
Reduction in HI from baseline during the post-treatment followup period	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	18/17 25.45	17/71 24.35	1.0 (0.6 to 1.9)	0.01 (-0.13 to 0.15)
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	29/34 40.85	34/71 48.65	0.8 (0.6 to 1.2)	-0.08 (-0.24 to 0.09)
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)	Amitriptyline 100mg/day	31/34 40.35	34/77 48.65	0.8 (0.6 to 1.2)	-0.08 (-0.24 to 0.08)
Reduction in HI from baseline during the post-treatment followup period	**Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)**	**Amitriptyline 100mg/day**	**32/17 41.65**	**17/77 24.35**	**1.7 (1.0 to 2.8)**	**0.17 (0.02 to 0.32)**
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	31/29 40.35	29/77 40.85	1.0 (0.7 to 1.5)	-0.01 (-0.16 to 0.15)
Reduction in HI from baseline during the post-treatment followup period	**Spinal Manipulation**	**Spinal Manipulation + Amitriptyline 100mg/day**	**32/18 41.65**	**18/77 25.45**	**1.6 (1.0 to 2.6)**	**0.16 (0.01 to 0.31)**

Bold- significant differences at 95% confidence limit; CI – confidence interval

Appendix Table D96. Strength of evidence of comparative effectiveness of antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial, [188]

Definition of the outcome	Active treatment	Control treatment	Risk of bias	Directness	Consistency	Precision	Strength of evidence
>60% reduction in HI in last 4 weeks of treatment phase	Spinal Manipulation	Amitriptyline 100mg/day	Moderate	Yes	NA	No	Low
>60% reduction in HI during the 4-week post-treatment follow-up phase	Spinal Manipulation	Amitriptyline 100mg/day	Moderate	Yes	NA	No	Low
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	Moderate	Yes	NA	No	Low
Reduction in HI from baseline during the post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	Moderate	Yes	NA	No	Low

Appendix Table D97. Comparative effectiveness of drugs with nonpharmacological treatments for migraine prevention in adults, randomized controlled clinical trials

Reference Country Sample	Drug	Aim	Definition of migraine	Concurrent medication	Age % women Baseline status of subjects
Nelson, 1998[188] Country: USA Sample: 218	Amitriptyline	To measure the relative efficacy of amitriptyline, spinal manipulation and the combination of both therapies for the prophylaxis of migraine headache.	International Headache Society criteria	None	Age Mean 37.9 years; % women 78.9 Migraine interfered substantially with work (% of patients): Amitriptyline group: 47.2; SMT group: 41.6; Combined treatment: 46.5 Days with headache (% of possible days during past month):Amitriptyline group: 54.5; SMT group: 53.3; Combined treatment: 50.8 Headache Index (mean diary score (0-70) during the 1-month baseline period): Amitriptyline group: 18.2(9.8); SMT group: 18.2 (9.1); Combined treatment: 10.1 (7.0)
Holroyd, 1995[189] Country: Not reported Sample: 33	Beta-blocker	To evaluate the ability of propranolol to enhance results achieved with relaxation-biofeedback training	International Headache Society diagnostic criteria (Headache Classification Committee of the IHS, 1988)	None	Age Mean 31.7 years; % women 79 Mean years of problem headache: 15.2 years (range, 1-47)
Streng, 2006[190] Country: Germany Sample: 114	Beta-blocker	To investigate whether acupuncture is as effective and safe as metoprolol in the prophylactic treatment migraine under conditions similar to routine care.	International Headache Society criteria	None	Age Mean 40.1 years; % women 87.72 Days with migraine, Mean (SD): Acupuncture: 5.8 (2.5); Metoprolol: 5.8 (2.9) Number of migraine attacks, Mean (SD): Acupuncture: 3.0 (1.4); Metoprolol:2.9 (1.3)
Seng, 2010[191] Country: USA Sample: 232	Beta-blocker	To examine expectancy changes with various combinations of Behavioral Migraine Management and migraine drug therapy	International Classification of Headache Disorders	Rescue drugs such as steroids were allowed	Age Mean 39.1 years; % women 79 Migraine days/30 days, mean (SD): 8.8 (11.5)
Holroyd, 2010[192] Country: USA Sample: 232	Beta-blocker	To determine if the addition of preventive drug treatment (β blocker), brief behavioral migraine management, or their combination improves the outcome of optimized acute treatment in the management of frequent migraine.	International Classification of Headache Disorders	Rescue drugs such as steroids were allowed	Age Mean 38.3 years; % women 79 Mean (SD) migraine days/30 days: Optimized acute treatment + placebo:8.4 (3.5); Optimized acute treatment + β blocker: 8.6 (3.3); Optimized acute treatment plus behavioral migraine management +placebo: 8.1 (3.4); Optimized acute treatment plus behavioral migraine management +β blocker: 8.7 (4.0)

Appendix Table D98. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of drugs and nonpharmacological migraine preventive treatments in adults

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Disclosed relationships
Nelson, 1998[188]	Grant	Yes	Yes	Not reported	Not applicable
Holroyd, 1994[189]	Grant	Not reported	Yes	Not reported	Not applicable
Streng, 2006[190]	Other	Yes	Yes	None	Not applicable
Seng, 2010[191]	Grant	Yes	Yes	Yes	Ms. Seng reports no conflicts of interest. Dr. Holroyd has received support from the National Institutes of Health (NINDS; NS32375), has consulted for ENDO Pharmaceuticals and Takeda Pharmaceuticals North America, and received an investigator initiated grant from ENDO Pharmaceuticals.
Holroyd, 2010[192]	Grant	Yes	Yes	Yes	KA Holroyd has consulted for ENDO Pharmaceuticals and for Takeda Pharmaceuticals North America and received an investigator initiated grant from ENDO Pharmaceuticals. He has also received support from the National Institutes of Health (NINDS; NS32375). CK Cottrell has received research funding and materials from GlaxoSmithKline Pharmaceuticals (GSK) and Merck and participates in industry sponsored research involving GSK, Merck, UCB Pharma, and Allergan. FJ O'Donnell has received research funding and materials from GSK and Merck; receives educational funding from GSK, Merck, and Allergan; participates in industry sponsored research involving GSK, Merck, UCB Pharma, and Allergan; and has consulted for and received honorariums from GSK. GE Corfingley owns stock in Johnson and Johnson, Novartis, and Wyeth Pharmaceuticals.
Wang, 2011[193]	Other	Yes	Yes	None	Not applicable
Dahlof, 1987[194]	Not reported	Not reported	Yes	Not reported	Not applicable

Appendix Table D99. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of drugs and nonpharmacological migraine preventive treatments in adults

Reference	Masking of the treatment status	Masking - outcome assessment	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Baseline similarity	Selective outcome reporting	Risk of bias
Nelson, 1998[188]	Open-label	Not reported	Yes	Unclear	Yes	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Moderate
Holroyd, 1995[189]	Open-label	Not reported	No	Unclear	Not reported	Not reported	Unclear	High
Streng, 2006[190]	Open-label	Outcome evaluators were blinded	Yes	Clearly Adequate	No (there was a significant difference between the groups for the scale for sensoric pain of the SES)	Frequency: similar; Severity: not reported; Duration: not reported	Unclear	High
Seng, 2010[191]	Double-blind	Not reported	No	Unclear	Yes	Not reported	Unclear	Moderate
Holroyd, 2010[192]	Double-blind for the drug and not for behavioral migraine management	Not reported	Yes	Unclear	Not reported The optimized treatment+beta-blocker group had migraine with current frequency for fewer number of years as compared to other groups	Not reported	Unclear	Low
Wang, 2011[193]	Single-blind	The outcome measurements were evaluated by blinded assessors who were unaware of patient allocation	Yes	Clearly adequate	Yes	Not reported	Unclear	Low
Dahlof, 1987[194]	Open-label	The analysis of the diary data was conducted by blind operators who did not know the group of each patient.	No	Unclear	Yes	Frequency: similar Severity: similar; Duration: not reported	Unclear	Moderate

Appendix Table D100. Migraine prevention with beta-blockers combined with behavior therapy vs. placebo in adults, results from individual low risk of bias randomized controlled clinical trial[192]

Definition of the outcome	Active treatment	Events/ randomized with active treatment	Events/ randomized with placebo	Rate of outcome, % in active group [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)**	**53/69**	**8/21**	**76.8[40.0]**	**2.0 (1.2 to 3.5)**	**0.39 (0.16 to 0.62)**
Dropped due to lack of efficacy	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	1/69	2/21	1.4 [7.3]	0.2 (0.0 to 1.6)	-0.08 (-0.21 to 0.05)
Dropped due to side effects	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	6/69	2/21	8.7 [9.1]	0.9 (0.2 to 4.2)	-0.01 (-0.15 to 0.13)
Dropped out	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	24/69	9/21	34.8 [41.8]	0.8 (0.4 to 1.5)	-0.08 (-0.32 to 0.16)

Bold-significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D101. Strength of evidence - efficacy and safety of beta-blockers combined with behavioral therapy (orientation + relaxation training; migraine warning signs and triggers; effectively using migraine medication and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. placebo for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[192]

Definition of the outcome	Active treatment	Control treatment	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Placebo	Propranolol/nadolol	Low	Yes	NA	No	Low
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	Low	Yes	NA	No	Low
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	Low	Yes	NA	No	Low

Appendix Table D102. Efficacy of beta-blockers combined with behavioral therapy (orientation + relaxation training; migraine warning signs and triggers; effectively using migraine medication and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. placebo for migraine prevention in adults, results from individual moderate risk of bias randomized controlled clinical trial[191]

Definition of the outcome	Active treatment	Randomized for active treatment [placebo]	Mean [standard deviation] with active treatment	Mean [standard deviation] with placebo	Mean difference (95% CI)	Standardized mean difference (95% CI)
Mean HSE (Headache Management Self-Efficacy Scale) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**144.8 [23.6]**	**117.2 [18.6]**	**27.6 (20.2 to 35.0)**	**1.3 (0.9 to 1.7)**
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**63.9 [7.7]**	**55.5 [9.5]**	**8.4 (5.3 to 11.5)**	**1.0 (0.6 to 1.4)**
Mean Chance HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**21.1 [8.4]**	**30.7 [8.5]**	**-9.6 (-12.6 to -6.6)**	**-1.1 (-1.5 to -0.8)**
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**31.6 [6.9]**	**35.4 [6.5]**	**-3.8 (-6.2 to -1.4)**	**-0.6 (-0.9 to -0.2)**

Bold significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D103. Comparative effectiveness of antidepressant amitriptyline, 100mg/day and spinal manipulation on intermediate outcomes in adults with migraine, individual moderate risk of bias randomized controlled clinical trial[188]

Definition of the outcome	Active treatment	Control treatment	Mean [standard deviation] with active treatment	Mean [standard deviation] with drug	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
HI (Headache Index): mean of last 4 week of the treatment period	Spinal Manipulation The spinal manipulation administered was a type described as high-velocity, low-amplitude, and short-lever arm.	Amitriptyline 100mg/days	9.8 [6.3]	9.1 [6.3]	0.7 (-1.3 to 2.7)	0.1 (-0.2 to 0.4)
HI (Headache Index): mean of last 4 week of the treatment period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	9.8 [6.3]	9.1 [6.3]	0.7 (-1.4 to 2.8)	0.1 (-0.2 to 0.4)
HI (Headache Index): mean during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	12.6 [7.0]	12.6 [7.0]	0.0 (-2.3 to 2.3)	0.0 (-0.3 to 0.3)
HI (Headache Index): mean during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	12.6 [7.0]	12.6 [7.0]	0.0 (-2.3 to 2.3)	0.0 (-0.3 to 0.3)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation	Amitriptyline 100mg/days	1.1 [1.1]	0.9 [1.0]	0.2 (-0.1 to 0.5)	0.2 (-0.1 to 0.5)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	1.1 [1.1]	0.9 [1.0]	0.2 (-0.1 to 0.5)	0.2 (-0.1 to 0.5)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	1.1 [1.3]	1.4 [1.3]	-0.3 (-0.7 to 0.1)	-0.2 (-0.6 to 0.1)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day		1.2 [1.5]	1.4 [1.3]	-0.2 (-0.7 to 0.3)	-0.1 (-0.5 to 0.2)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	73.6 [10.7]	71.2 [10.5]	2.4 (-1.0 to 5.8)	0.2 (-0.1 to 0.6)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	72.9 [10.5]	71.2 [10.5]	1.7 (-1.8 to 5.2)	0.2 (-0.2 to 0.5)

Appendix Table 103. Comparative effectiveness of antidepressant amitriptyline, 100mg/day and spinal manipulation on intermediate outcomes in adults with migraine, individual moderate risk of bias randomized controlled clinical trial[187] (continued)

Definition of the outcome	Active treatment	Control treatment	Mean [standard deviation] with active treatment	Mean [standard deviation] with drug	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
HI (Headache Index) : mean of last 4 week of the treatment period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	9.8 [6.3]	9.8 [6.3]	0.0 (-2.0 to 2.0)	0.0 (-0.3 to 0.3)
HI (Headache Index) : mean during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	9.8 [7.0]	12.6 [7.0]	-2.8 (-5.1 to -0.5)	-0.4 (-0.7 to -0.1)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	1.1 [1.1]	1.1 [1.1]	0.0 (-0.4 to 0.4)	0.0 (-0.3 to 0.3)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	1.1 [1.3]	1.2 [1.5]	-0.1 (-0.6 to 0.4)	-0.1 (-0.4 to 0.3)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	73.6 [10.7]	72.9 [10.5]	0.7 (-2.7 to 4.1)	0.1 (-0.3 to 0.4)

CI – confidence interval

Appendix Table D104. Dose response in acute treatment utilization with botox for migraine prevention in adults (individual low risk of bias RCT)[10]

Outcome	Dose of botox in active vs. control, units	Events/randomized with larger dose	Events/randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Patients using and overusing acute headache pain medications	225 vs. 150	144/182	152/168	0.9 (0.8 to 1.0)	**-0.11 (-0.19 to -0.04)**
Patients using and overusing acute headache pain medications	225 vs. 150	151/182	157/168	0.9 (0.8 to 1.0)	**-0.10 (-0.17 to -0.04)**

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D105. Dose response in global assessment of treatment success with botox for migraine prevention in adults (individual low risk of bias RCT)[7]

Outcome	Dose of botox in active vs. control, units	Events/randomized with larger dose	Events/randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Improvement in global assessment (patient score) week 4-8	240 vs. 120	11/43	14/43	0.8 (0.4 to 1.5)	-0.07 (-0.26 to 0.12)
Improvement in global assessment (investigator score) week 4-8	240 vs. 120	12/43	11/43	1.1 (0.5 to 2.2)	0.02 (-0.16 to 0.21)
Improvement in global assessment (patient score) week 4-12	240 vs. 120	16/43	16/43	1.0 (0.6 to 1.7)	0.00 (-0.20 to 0.20)
Improvement in global assessment (investigator score) week 4-12	240 vs. 120	17/43	18/43	0.9 (0.6 to 1.6)	-0.02 (-0.23 to 0.18)

CI – confidence interval

Appendix Table D106. Dose response reduction in migraine attacks for at least 50% from baseline with topiramate in adults

Reference	Active dose	Control dose	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Brandes, 2004[21]	100mg/day	50mg/day	1.3 (0.9 to 1.7)	33.7	0.10 (-0.02 to 0.23)	32.30
Silberstein, 2003[20]	100mg/day	50mg/day	1.5 (1.1 to 2.1)	31.9	0.19 (0.07 to 0.31)	33.27
Silberstein, 2004[22]	100mg/day	50mg/day	1.5 (1.1 to 2.0)	34.5	0.18 (0.06 to 0.30)	34.43
Pooled, random effects model, inverse variance	**100mg/day**	**50mg/day**	**1.4 (1.2 to 1.7)**	**100.0**	**0.16 (0.09 to 0.23)**	**100**
Brandes, 2004[21]	200mg/day	100mg/day	1.0 (0.7 to 1.2)	29.42	-0.02 (-0.15 to 0.11)	33.49
Silberstein, 2003[20]	200mg/day	100mg/day	1.0 (0.8 to 1.2)	34.63	-0.02 (-0.15 to 0.11)	32.75
Silberstein, 2004[22]	200mg/day	100mg/day	1.0 (0.8 to 1.2)	35.95	-0.02 (-0.14 to 0.11)	33.77
Pooled, random effects model, inverse variance	**200mg/day**	**100mg/day**	**1.0 (0.8 to 1.1)**	**100**	**-0.02 (-0.09 to 0.05)**	**100**
Brandes, 2004[21]	200mg/day	50mg/day	1.2 (0.9 to 1.6)	34.17	0.08 (-0.05 to 0.20)	33.49
Silberstein, 2003[20]	200mg/day	50mg/day	1.5 (1.1 to 2.0)	31.43	0.17 (0.04 to 0.29)	32.44
Silberstein, 2004[22]	200mg/day	50mg/day	1.4 (1.1 to 1.9)	34.4	0.16 (0.04 to 0.29)	34.07
Pooled, random effects model, inverse variance	**200mg/day**	**50mg/day**	**1.4 (1.2 to 1.6)**	**100**	**0.14 (0.06 to 0.21)**	**100**

Bold - significant differences at 95% confidence limit
CI - confidence interval

Appendix Table D107. Dose response migraine prevention with divalproex in adults, results from low risk of bias randomized controlled clinical trial[45]

Outcome	Daily doses of divalproex	Events/ randomized with larger dose	Events/ randomized with smaller dose	Relative risk	Absolute risk difference (95% CI)	Attributable events per 1000 treated (95% CI)
50% improvement in migraine attacks impairing usual activities	**1000 mg vs. 500 mg**	**16/43**	**26/45**	**0.6 (0.4 to 1.0)**	**-0.21 (-0.41 to 0.00)**	**-206 (-410 to -1)**
50% improvement in migraine attacks impairing usual activities	1500 mg vs. 500 mg	24/44	26/45	0.9 (0.7 to 1.4)	-0.03 (-0.24 to 0.17)	NS
50% improvement in migraine attacks impairing usual activities	1500 mg vs. 1000 mg	24/44	16/43	1.5 (0.9 to 2.4)	0.17 (-0.03 to 0.38)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg vs. 500 mg	16/43	19/45	0.9 (0.5 to 1.5)	-0.05 (-0.25 to 0.15)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg vs. 500 mg	19/44	19/45	1.0 (0.6 to 1.7)	0.01 (-0.20 to 0.22)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg vs. 1000 mg	19/44	16/43	1.2 (0.7 to 1.9)	0.06 (-0.15 to 0.27)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1000 mg vs. 500 mg	18/43	21/45	0.9 (0.6 to 1.4)	-0.05 (-0.26 to 0.16)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1500 mg vs. 500 mg	22/44	21/45	1.1 (0.7 to 1.6)	0.03 (-0.17 to 0.24)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1500 mg vs. 1000 mg	22/44	18/43	1.2 (0.8 to 1.9)	0.08 (-0.13 to 0.29)	NS

Bold - significant at 95% confidence limit; CI – confidence level; NS – not significant

Appendix Table D108. Migraine management programs examined in randomized controlled clinical trials

Reference Country Sample	Aim	Definition of migraine	Concurrent medication	Age of subjects (mean or median) % women Baseline migraine severity
Lemstra, 2002[195] Country: Not reported Sample: 80	To test the effectiveness of a multidisciplinary management program for migraine treatment in a group, low-cost, nonclinical setting	International Headache Society criteria	Not reported	Mean 34.5 years 66.3% women Average pain in last month (1-10): Intervention: 7.34+-1.87, Control: 7.14+-2.02 Pain Disability Index: Intervention: 32.95+-12.92, Control: 34.19+-16.06
Matchar, 2008[196] Country: USA Sample: 614	To determine of patients cared for in a coordinated headache management program would achieve reduced headache disability compared with patients in usual care	Not reported	Not reported	Mean 43.5 years 87% women MIDAS, mean (SD): 48.8 (64.0)
Rothrock, 2006[197] Country: USA Sample: 100	To determine whether the addition of patient education to routine medical management improves the clinical status of migraine patients and reduces their utilization of healthcare resources.	International Headache Society criteria	Prophylactic medication was prescribed to all "school" patients and to 41 (82%) of the "no school" patients: antiepileptic drug or gabapentin.	Mean 42.5 years 92% women Mean headache days: intervention=14, control=23
Fritsche, 2010[198] Country: Germany Sample: 158	To compare the therapeutic effect of a cognitive-behavioral minimal contact program (MCT) to the effect of a brochure (bibliotherapy) for the prevention of medication overuse headache (MOH) in migraine patients.	ICHD-II criteria	Not reported	Mean 48 years 91% women Migraine days, mean (SD):MCT=7.23 (3.70), bibliography=7.27 (3.82); Headache disability, mean (SD): MCT=4.46 (1.80), bibliography=4.16 (1.56)
Sondergaard, 2006[199] Country: Denmark Sample: 2463	To evaluate the impact of an intensive pharmaceutical care campaign targeting inappropriate use of triptans	Not reported	Triptans	Median:Intervention: 47 years, Control: 46 years 83% women Baseline severity not reported
Hoffmann, 2008[200] Country: Germany Sample: 410	To evaluate the effects of pharmaceutical care (defined as intensified structured counseling between patient and pharmacist, including the use of drug databases), for patients with headache or migraine, on both clinical and psychological endpoints.	Criteria of the International Headache Society (HIS) and the Kiel Headache Questionnaire	Not reported	Mean 43,3 years 83% women Headache attacks/month, n: Intervention group: 5.12±7.29, Control group: 4.81±5.65 Treated: Intervention group: 27.43±70.27, Control group: 22.37±56.87 Intensity of headache pain: Untreated: Intervention group: 8.38±1.52, Control group: 8.45±1.61

Appendix Table D109. Funding and conflict of interest in randomized controlled clinical trials that examined migraine management programs in adults

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Disclosed relationships
Lemstra, 2002[195]	Not reported	Yes	Yes	Not reported	Not applicable
Matchar, 2008[196]	Grant	Yes	Yes	Yes	Richard Lipton has consulted for, conducted studies funded by, and/or received lecture honoraria from Advanced Bionics, Allergan, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cierra, Endo, GlaxoSmithKline, Merck, Neualieve, Ortho-McNeil, Pfizer, Pozen, ProEthics and St Judes. The following authors have no conflict of interest. Including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript: David B. Matchar, Gregory Samsa, Annette Jurgelski. Dr.Harpole and Kori are presently employees of GlaxoSmithKline.
Rothrock, 2006[197]	Not reported	Yes	Yes	Not reported	Not applicable
Fritsche, 2010[198]	Grant	Yes	Yes	None	Not applicable
Sondergaard, 2006[199]	Grant	Yes	Not reported	Not reported	Not applicable
Hoffmann, 2008[200]	Industry + Other	Yes	Yes	Not reported	Not reported, however, Michael Cramer is the Head of Division for Pharmacies and Health Provision, Ministry for Work, Social, Health, Family and Gender Issues, Mainz, Germany. Doris Gresselmeyer is a pharmacist from Linden - Apotheke, Bremen, Germany

Appendix Table D110. Risk of bias in randomized controlled clinical trials that examined migraine management programs in adults

Reference	Masking of the treatment status	Masking - outcome assessment	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Groups Similarity	Risk of bias
Lemstra, 2002[195]	Open-label (Therapists were blind as to which specific outcome variables were primarily under evaluation).	The outcome assessor was blind to the intervention status.	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: not reported	Moderate
Matchar, 2008[196]	Not reported	Yes	No	Unclear	Not adequate	Frequency: not reported; Severity: similar (MIDAS score include headache days and severity of pain and they were similar across the groups); Duration: not reported	Moderate
Rothrock, 2006[197]	Not reported	Yes	No	Unclear	Not adequate : difference in episodic migraine in control group (36% vs. 2%); frequent episodic migraine (72% vs. 28%); and mean MIDAS score was lower in the intervention group	Not reported	Moderate
Fritsche, 2010[198]	Not reported	Not reported	No	Clearly adequate (central randomization)	Not reported (There were no patients with aura in the control group)	Frequency: similar; Severity: similar; Duration: not reported	Low
Sondergaard, 2006[199]	Not reported	Not reported	Not reported	Unclear	Yes	Not reported	Low
Hoffman, 2008[200]	Not reported	Not reported	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Low

Appendix Table D111. Description of disease management programs for migraine prevention in adults

Reference	Program	Description	Control	Description
Lemstra, 2002[195]	Multidisciplinary intervention: It consisted of a neurologist intake, physical therapist intake, 18 group-supervised exercise therapy sessions with an exercise therapist, 2 group lectures with a registered psychologist 1 group lecture with a dietitian, 2 massage therapy sessions, and a neurologist and physical therapist discharge. The initial neurologist evaluation was intended to confirm the diagnosis, obtain a detailed history, and confirm appropriateness to participate. The physical therapist provided a detailed biomechanical evaluation, provided education on hurt versus harm, identified barriers to participation, and initiated an action plan to prevent dropout. The exercise therapist supervised the exercise therapy sessions, which included submaximal aerobic exercise, stretching, and light weight training, and monitored attendance and created a social no intimidating environment for the patients. The psychologist provided 1 group lecture on relaxation training and another on behavioral modification and stress management. The dietitian provided 1 group lecture on general dietary goals and explained how to substitute alternatives to potential dietary triggers. The massage therapist provided 2 individual sessions with the goal of relaxation and a means of reward after initial exercise sessions rather than any type of therapeutic benefit.	Multidisciplinary intervention: It consisted of a neurologist intake, physical therapist intake, 18 group-supervised exercise therapy sessions with an exercise therapist, 2 group lectures with a registered psychologist 1 group lecture with a dietitian, 2 massage therapy sessions, and a neurologist and physical therapist discharge. The initial neurologist evaluation was intended to confirm the diagnosis, obtain a detailed history, and confirm appropriateness to participate. The physical therapist provided a detailed biomechanical evaluation, provided education on hurt versus harm, identified barriers to participation, and initiated an action plan to prevent dropout. The exercise therapist supervised the exercise therapy sessions, which included submaximal aerobic exercise, stretching, and light weight training, and monitored attendance and created a social no intimidating environment for the patients. The psychologist provided 1 group lecture on relaxation training and another on behavioral modification and stress management. The dietitian provided 1 group lecture on general dietary goals and explained how to substitute alternatives to potential dietary triggers. The massage therapist provided 2 individual sessions with the goal of relaxation and a means of reward after initial exercise sessions rather than any type of therapeutic benefit.	Standard medical care with the patient's family physician	Standard medical care with the patient's family physician

Appendix Table 111. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
Matchar, 2008[196]	Headache management program: This involved developing a set of general functional specifications for a headache program, identifying local site-specific barriers to implementing the functional specifications, and working with investigators to develop a set of mutually acceptable tools that assured comparability and standardization across sites. The intervention was administered by a mid-level provider (e.g. nurse practitioner or PA) with expertise in headache evaluation and management. The program included an educational session attended by all intervention patients either individually or as a group (the headache class). Patients were given educational materials that included information on headache types and etiologies, pharmacologic treatment, triggers, sleep hygiene, and relaxation techniques.	Headache management program consisting of :1) a class specifically designed to inform patients about headache types, triggers, and treatment options; 2) diagnosis and treatment by a professional especially trained in headache care (based on US Headache Consortium guidelines); and 3) proactive follow-up by a case-manager. It also included an educational session attended by all intervention patients either individually or as a group; an initial visit to the clinic for evaluation; and follow-up visits (in-person or by telephone) at 1, 3, and 6 months.	Usual care	Continue with current clinician and no access to the headache management program
Fritsche, 2010[198]	Cognitive-behavioral minimal contact program (MCT)	It consisted of 5 sessions with sic participants and lasting 2 hours (2*50min plus 20-min plus a 20-min break) each. The first unit (session) was called "Introduction and syndrome education". It main components included information about symptoms, pathophysiology and pathopsychology of migraine as well as instructions for progressive muscle relaxation (PMR). The 2nd unit was called "Medication rules and the risk of Medication Overuse Headache" including information about acute and prophylactic migraine medication and medication overuse headache-symptoms and patho-mechanisms. The 3rd unit was called "Medication intake behavior" aimed at raising awareness for "external" (e.g. availability of drugs, stock-keeping, iatrogenic risk factors like doctor shopping) and "internal" (e.g. fear of attack and losing social functioning, stress level in private and professional life) influences on patient's medication intake behavior. The 4th	Brochure (bibliography)	The participants received two brochures: a detailed brochure as a patient guide with information about physiological and psychological aspects of migraine, medication-overuse headache and migraine medication. It summarized the topics which were covered by the MCT, written in the style of a self-help manual containing instructions for exercises to minimize drug consumption and instructions for PMR. Each chapter of the brochure ended with questions about the

Appendix Table 111. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
		unit was called "general and personal risk factors for drug intake" and established a general risk profile of medication overuse for each patient. The 5th unit was called "everyday transfer" with the aim of establishing individual goals for future drug intake and learning how to make use of social support to control intake behavior. At the end of the 5th session, participants received the brochures given to the biblio-group.		content of the chapter which the patients were to answer. The brochure was called ‘‘Migraine and medication – Which problems can arise and what to do”. The second brochure (extended information about migraine medication) contained information material without any exercise instructions. Part one of the brochure described the indication, the pharmacological mechanisms of action and the side-effects of different acute migraine medications, and part two discussed prophylactic medication. There was no face-to-face contact and the participants had the opportunity to obtain advice by telephone if they had any questions regarding the brochures.
Rothrock, 2006[197]	Standardized course of didactic instructions regarding migraine biogenesis and management ("headache school")	The curriculum consisted of 3 90-minute classes held on evenings and weekends and taught by lay migraineurs who previously had undergone intensive classroom and in-clinic training by 1 of the neurology investigators (Johns Rothrock).The 3 “headache school” classes primarily involved the topics of migraine biogenesis, acute treatment of migraine, and prevention of migraine. Working together, in each class 2 instructors provided 30 to 45 minutes of didactic instruction, followed by a review of hard copy materials related to the primary topic and permanently provided to the participants, demonstration of therapeutic devices (e.g., the autoinjector used to administer sumatriptan; subcutaneous administration of dihydroergotamine via a 1 cc syringe and 27 g needle), and, to close, an interactive question and answer session cum open forum. All individuals serving as patient instructors underwent 12 hours of classroom instruction in headache theory and treatment, received and reviewed a	Routine medical management	

Appendix Table 111. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
		related course syllabus, were required to pass successfully a written examination based on that didactic instruction, and then served a minimum of 12 hours as observers in the headache clinics.		
Hoffmann, 2008[200]	Pharmaceutical care for migraine	Pharmacists from the intervention pharmacies participated in a 2-day central training program conducted by a physician and a pharmacist who were employees of the university. Together with the patient, the intervention pharmacist prioritized problems, defined goals, and devised a plan to work toward them. The training was based on a comprehensive standard operation manual that was distributed to the intervention pharmacists upon completion of the program. The manual was developed by the Federal Union of German Associations of Pharmacists, in cooperation with the principal investigators, and contains central definitions of pharmaceutical care (PC),with a focus on PC in patients with different types of pain (e.g., headache, muscle).	Standard counseling	Patients received the regular pharmaceutical consultation; their pharmacists were not specially trained, did not receive the standard manual, and were not included in the documentation scheme for counseling. This regular counseling includes general information about application and possible adverse drug effects.
Sondergaard, 2006[199]	Intensive pharmaceutical care campaign	Pharmacists from the intervention pharmacies provided the intervention. They were encouraged to involve the pharmacy assistants. A manual given to pharmacy staff described how to identify inappropriate triptan use, how to establish a dialogue and how to ask questions. Moreover, it offered suggestions for relevant questions, advice, literature on headache, migraine and pharmaceutical care, and included a checklist. The training package was developed in cooperation with the Danish College of Pharmacy Practice (Pharmakon). When presenting a triptan prescription at the pharmacy, the user received a folder designed to support the dialogue and assist the pharmacist in detecting triptan overuse. It included information on the campaign and questions on the patient's drug use, e.g. the type of headache for which the patient used triptans, monthly consumption of triptans, repeated use of triptans even if the first dose had no effect on the attack, and the frequency of use of other types of painkillers. The dialogue between the pharmacist and the patient took place immediately after the folder had been read and its questions answered. To ensure an undisturbed, confidential conversation, the pharmacies were encouraged to let the dialogue with triptan users take place in a separate room. Each dialogue was estimated to last on average 15 minutes and each triptan user participated only once.	Control pharmacy	

Appendix Table D112. Adherence to multidisciplinary intervention for migraine prevention in adults compared to standard care, results from moderate risk of bias randomized controlled clinical trial[195]

Definition of the outcome	Events/randomized with multidisciplinary intervention	Events/randomized with usual care	Relative risk (95% CI)	Absolute risk difference (95% CI)
Quit intervention due to inefficiency	1/44	0/36	2.5 (0.1to 58.8)	0.02 (-0.04 to 0.09)
Quit intervention	3/44	0/36	5.8 (0.3to 107.9)	0.07 (-0.02 to 0.15)

CI – confidence interval

Appendix Table D113. Effectiveness of multidisciplinary intervention for migraine prevention in adults compared to standard care (results from moderate risk of bias randomized controlled clinical trial)[195]

Definition of the outcome at 3 months of followup after the intervention	Mean [standard deviation] with multidisciplinary intervention	Mean [standard deviation] with usual care	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
% change in self-perceived pain frequency (Visual Analogue Scale that included values from 100% worse to 100% improvement)	56.9 [9.1]	-2.2 [2.2]	59.15 (56.36 to 61.94)	8.5 (7.1 to 9.9)
% change in pain intensity (Visual Analogue Scale that included values from 100% worse to 100% improvement)	38.2 [8.5]	-2.8 [2.0]	40.96 (38.36 to 43.56)	6.3 (5.2 to 7.4)
% change in pain duration (Visual Analogue Scale that included values from 100% worse to 100% improvement)	47.2 [8.3]	-5.0 [2.9]	52.16 (49.52 to 54.80)	8.0 (6.7 to 9.4)
% change in functional status (Visual Analogue Scale that included values from 100% worse to 100% improvement)	51.6 [7.7]	-0.6 [2.0]	52.15 (49.78 to 54.52)	8.9 (7.4 to 10.3)
% change in quality of life (Visual Analogue Scale that included values from 100% worse to 100% improvement)	57.1 [8.2]	-1.9 [1.9]	58.99 (56.49 to 61.49)	9.5 (8.0 to 11.1)
% change in Pain Disability Index (Visual Analogue Scale that included values from 100% worse to 100% improvement)	18.8 [2.2]	1.7 [1.0]	17.08 (16.35 to 17.81)	9.6 (8.0 to 11.2)
% change in Beck Depression Inventory (Visual Analogue Scale that included values from 100% worse to 100% improvement)	10.6 [1.3]	1.2 [0.5]	9.44 (9.04 to 9.84)	9.7 (8.1 to 11.2)

Bold - significant differences at 95% CI
CI – confidence interval

Appendix Table D114. Reduction in disability with headache management program for migraine prevention in adults compared to standard care (results from moderate risk of bias randomized controlled clinical trial)[196]

Definition of the outcome	Events/randomized with headache management program	Events/randomized with usual care	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
6 months: Achieved a MIDAS score of 0 reflecting no headache-related disability	124/305	65/309	1.9 (1.5to 2.5)	0.20 (0.12 to 0.27)	5 (4 to 8)	196 (125 to 258)

CI – confidence interval

Appendix Table D115. Effectiveness of headache management program for migraine prevention in adults compared to standard care (results from moderate risk of bias randomized controlled clinical trial)[196]

Definition of the outcome	Mean [standard deviation] with headache management program	Mean [standard deviation] with usual care	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
MIDAS score at 6 months	**15.9 [24.4]**	**23.6 [37.6]**	**-7.70 (-12.71 to -2.69)**	**-0.2 (-0.4 to -0.1)**
Quality of life (SF-36): Physical function domain	**84.0 [20.6]**	**79.0 [22.3]**	**5.00 (1.60 to 8.40)**	**0.2 (0.1 to 0.4)**
Quality of life (SF-36): Role physical domain	**75.7 [24.8]**	**67.5 [25.1]**	**8.20 (4.25 to 12.15)**	**0.3 (0.2 to 0.5)**
Quality of life (SF-36): Pain domain	**63.8 [23.0]**	**55.5 [22.5]**	**8.30 (4.70 to 11.90)**	**0.4 (0.2 to 0.5)**
Quality of life (SF-36): General health domain	53.3 [9.9]	52.3 [9.8]	1.00 (-0.56 to 2.56)	0.1 (-0.1 to 0.3)
Quality of life (SF-36): Vitality domain	**52.8 [21.4]**	**48.8 [19.3]**	**4.00 (0.78 to 7.22)**	**0.2 (0.0 to 0.4)**
Quality of life (SF-36): Social function domain	**73.4 [24.9]**	**68.7 [24.8]**	**4.70 (0.77 to 8.63)**	**0.2 (0.0 to 0.3)**
Quality of life (SF-36): Role emotional domain	**77.9 [24.1]**	**73.8 [25.6]**	**4.10 (0.17 to 8.03)**	**0.2 (0.0 to 0.3)**
Quality of life (SF-36): Mental health domain	69.7 [19.2]	66.8 [19.9]	2.90 (-0.19 to 5.99)	0.1 (0.0 to 0.3)
Quality of life (SF-36): Physical summary domain	**47.6 [7.7]**	**45.0 [8.4]**	**2.60 (1.33 to 3.87)**	**0.3 (0.2 to 0.5)**
Quality of life (SF-36): Mental summary domain	45.4 [11.6]	43.9 [11.6]	1.50 (-0.34 to 3.34)	0.1 (0.0 to 0.3)
General health (from 1[excellent] to 5 [poor])	**2.4 [0.9]**	**2.7 [0.9]**	**-0.30 (-0.44 to -0.16)**	**-0.3 (-0.5 to -0.2)**
Change since last year (from 1 [much better] to 5 [much worse])	**2.5 [0.9]**	**2.8 [0.9]**	**-0.30 (-0.44 to -0.16)**	**-0.3 (-0.5 to -0.2)**
Depression (PHQ-9) (Patient Health Questionnaire -Short Form)	**5.6 [5.2]**	**6.6 [5.3]**	**-1.00 (-1.83 to -0.17)**	**-0.2 (-0.3 to 0.0)**
MIDAS: Missed work days	1.2 [2.7]	1.6 [6.5]	-0.40 (-1.19 to 0.39)	-0.1 (-0.2 to 0.1)
MIDAS: Missed half work days	3.9 [7.9]	5.2 [8.8]	-1.30 (-2.62 to 0.02)	-0.2 (-0.3 to 0.0)
MIDAS: Missed house days	**5.0 [10.2]**	**7.1 [11.2]**	**-2.10 (-3.79 to -0.41)**	**-0.2 (-0.4 to 0.0)**
MIDAS: Missed half house days	**3.9 [6.0]**	**6.8 [10.5]**	**-2.90 (-4.25 to -1.55)**	**-0.3 (-0.5 to -0.2)**
MIDAS: Missed family days	**2.4 [4.9]**	**3.6 [8.1]**	**-1.20 (-2.26 to -0.14)**	**-0.2 (-0.3 to 0.0)**
MIDAS: Headache days	**13.8 [17.6]**	**17.7 [20.9]**	**-3.90 (-6.95 to -0.85)**	**-0.2 (-0.4 to 0.0)**
MIDAS: Headache pain (from 0 [no pain at all] to 10[pain as bad as it can be])	**5.6 [2.3]**	**6.1 [2.2]**	**-0.50 (-0.86 to -0.14)**	**-0.2 (-0.4 to -0.1)**
Worried about headache (from 0 [not worried at all] to 10 [extremely worried])	**4.4 [2.7]**	**5.1 [2.7]**	**-0.70 (-1.13 to -0.27)**	**-0.3 (-0.4 to -0.1)**
Problems with headache management (from 1 [no problems] to 4 [severe amount of problems])	**2.1 [0.8]**	**2.4 [0.7]**	**-0.30 (-0.42 to -0.18)**	**-0.4 (-0.6 to -0.2)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Headache care	**1.8 [1.0]**	**2.4 [1.2]**	**-0.60 (-0.77 to -0.43)**	**-0.5 (-0.7 to -0.4)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Understanding	**1.7 [1.0]**	**2.4 [1.2]**	**-0.70 (-0.87 to -0.53)**	**-0.6 (-0.8 to -0.5)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Medications	**2.0 [1.1]**	**2.5 [1.2]**	**-0.50 (-0.68 to -0.32)**	**-0.4 (-0.6 to -0.3)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Medical care in general	**1.7 [0.9]**	**2.0 [1.0]**	**-0.30 (-0.45 to -0.15)**	**-0.3 (-0.5 to -0.2)**

Bold - significant differences at 95% confidence limit; CI – confidence interval

Appendix Table D116. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from moderate risk of bias randomized controlled clinical trial)[198]

Definition of the outcome	Mean [standard deviation] with cognitive-behavioral minimal contact program	Mean [standard deviation] with educational brochure	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Headache days: 3 months after treatment	8.6 [5.5]	8.1 [4.8]	0.44 (-1.21 to 2.09)	0.1 (-0.2 to 0.4)
Headache days: 1-2 years after treatment	8.7 [5.3]	8.3 [5.2]	0.35 (-1.32 to 2.02)	0.1 (-0.3 to 0.4)
Migraine days: 3 months after treatment	6.2 [4.0]	5.5 [3.2]	0.70 (-0.44 to 1.84)	0.2 (-0.1 to 0.5)
Migraine days: 1-2 years after treatment	6.2 [4.0]	5.8 [3.8]	0.31 (-0.94 to 1.56)	0.1 (-0.2 to 0.4)
Headache disability: 3 months after treatment	4.6 [2.0]	4.3 [1.9]	0.36 (-0.26 to 0.98)	0.2 (-0.1 to 0.5)
Headache disability: 1-2 years after treatment	4.4 [2.2]	4.4 [1.7]	-0.01 (-0.63 to 0.61)	0.0 (-0.3 to 0.3)
Intake at headache days: 3 months after treatment	5.9 [3.2]	6.5 [3.2]	-0.54 (-1.57 to 0.49)	-0.2 (-0.5 to 0.2)
Intake at headache days: 1-2 years after treatment	6.2 [3.7]	6.0 [2.8]	0.18 (-0.86 to 1.22)	0.1 (-0.3 to 0.4)
Intake at migraine days: 3 months after treatment	4.8 [3.0]	4.8 [2.8]	0.08 (-0.85 to 1.01)	0.0 (-0.3 to 0.3)
Intake at migraine days: 1-2 years after treatment	5.0 [3.5]	5.0 [2.8]	0.01 (-1.00 to 1.02)	0.0 (-0.3 to 0.3)
CPAQ-AE ('Activity engagement' subscale of the "Chronic Pain Acceptance Questionnaire"): 3 months after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	34.6 [10.9]	34.9 [9.4]	-0.32 (-3.56 to 2.92)	0.0 (-0.4 to 0.3)
CPAQ-AE ('Activity engagement' subscale of the "Chronic Pain Acceptance Questionnaire"): 1-2 years after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	35.5 [10.8]	34.4 [9.4]	1.12 (-2.11 to 4.35)	0.1 (-0.2 to 0.4)
CPAQ-PW ('Pain willingness' subscale of the "Chronic Pain Acceptance Questionnaire"): 3 months after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	22.5 [8.9]	23.4 [8.0]	-0.89 (-3.58 to 1.80)	-0.1 (-0.4 to 0.2)
CPAQ-PW ('Pain Willingness' subscale of the "Chronic Pain Acceptance Questionnaire"): 1-2 years after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	26.8 [9.6]	25.2 [7.6]	1.55 (-1.21 to 4.31)	0.2 (-0.1 to 0.5)
FSS-CATA ('Catastrophising cognitions' subscale of the "Pain-related self instructions" questionnaire): 3 months after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	24.2 [7.3]	25.5 [7.3]	-1.33 (-3.67 to 1.01)	-0.2 (-0.5 to 0.1)
FSS-CATA ('Catastrophising cognitions' subscale of the "Pain-related self instructions" questionnaire): 1-2 years after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	21.4 [10.3]	22.1 [8.5]	-0.68 (-3.70 to 2.34)	-0.1 (-0.4 to 0.2)

Appendix Table 116. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from moderate risk of bias randomized controlled clinical trial)[197] (continued)

Definition of the outcome	Mean [standard deviation] with cognitive-behavioral minimal contact program	Mean [standard deviation] with educational brochure	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
FSS-FUNC ('Functional cognitions' subscale of the "Pain-related self instructions" questionnaire): 3 months after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	**34.2 [14.7]**	**29.8 [6.1]**	**4.32 (0.79 to 7.85)**	**0.4 (0.1 to 0.7)**
FSS-FUNC ('Functional cognitions' subscale of the "Pain-related self instructions" questionnaire): 1-2 years after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	29.5 [7.3]	29.2 [6.3]	0.33 (-1.84 to 2.50)	0.0 (-0.3 to 0.4)
HADS -A ('Anxiety 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 3 months after intervention.	6.2 [2.3]	6.4 [2.2]	-0.17 (-0.90 to 0.56)	-0.1 (-0.4 to 0.2)
HADS -A ('Anxiety 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 1-2 years after intervention.	5.9 [3.8]	6.2 [4.1]	-0.32 (-1.58 to 0.94)	-0.1 (-0.4 to 0.2)
HADS -D ('Depression 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 3 months after intervention.	4.8 [1.2]	4.8 [1.3]	0.03 (-0.37 to 0.43)	0.0 (-0.3 to 0.3)
HADS -D ('Depression 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 1-2 years after intervention.	4.8 [4.2]	4.9 [4.0]	-0.14 (-1.45 to 1.17)	0.0 (-0.4 to 0.3)
KKG-INT ('Internal control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	26.2 [5.3]	25.1 [4.4]	1.07 (-0.48 to 2.62)	0.2 (-0.1 to 0.5)
KKG-INT ('Internal control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	26.3 [4.3]	25.2 [4.9]	1.10 (-0.38 to 2.58)	0.2 (-0.1 to 0.6)
KKG-EXT ('External control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	21.0 [5.7]	21.2 [5.1]	-0.17 (-1.90 to 1.56)	0.0 (-0.4 to 0.3)
KKG-EXT ('External control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	21.0 [5.5]	20.7 [6.8]	0.26 (-1.73 to 2.25)	0.0 (-0.3 to 0.4)
KKG-FATA ('Fatalistic' subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	**16.8 [6.3]**	**19.5 [6.1]**	**-2.72 (-4.71 to -0.73)**	**-0.4 (-0.8 to -0.1)**
KKG-FATA ('Fatalistic' subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	18.5 [6.7]	18.4 [6.5]	0.10 (-2.03 to 2.23)	0.0 (-0.3 to 0.3)

Appendix Table 116. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from moderate risk of bias randomized controlled clinical trial)[197] (continued)

Definition of the outcome	Mean [standard deviation] with cognitive-behavioral minimal contact program	Mean [standard deviation] with educational brochure	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Satisfied with treatment (assessed in a telephone interview three months after the intervention. Patients rated the extent of helpfulness of the treatment in reducing medication intake and whether and to what extent they would recommend the treatment to a friend on a range of 1-6 (1=very good to 6=very bad)	**1.7 [0.6]**	**2.8 [1.0]**	**-1.10 (-1.37 to -0.83)**	**-1.3 (-1.7 to -1.0)**
Satisfied that treatment is helpful for reducing medication intake (assessed in a telephone interview three months after the intervention. Patients rated the extent of helpfulness of the treatment in reducing medication intake and whether and to what extent they would recommend the treatment to a friend on a range of 1-6 (1=very good to 6=very bad)	**1.9 [0.6]**	**2.6 [0.8]**	**-0.68 (-0.91 to -0.45)**	**-1.0 (-1.3 to -0.6)**

Bold-significant differences at 95% CL
CI – confidence interval

Appendix Table D117. Reduction in acute drug overuse with headache school for migraine prevention in adults on acute drug utilization (results from moderate risk of bias randomized controlled clinical trial)[197]

Definition of the outcome	Events/randomized with headache school	Events/randomized with usual care	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Analgesic overuse: at 6 months (number of patients using a given abortive agent or class of abortive agents >3 days/week for >4 weeks)	**0/50**	**18/50**	**0.0 (0.0to 0.4)**	**-0.36 (-0.49 to -0.23)**	**-3 (-4- to -2)**	**360 (225 to 495)**

Bold-significant differences at 95% CI
CI – confidence interval

Appendix Table D118. Effectiveness of headache school for migraine prevention in adults (results from moderate risk of bias randomized controlled clinical trial)[197]

Definition of the outcome	Mean [standard deviation] with headache school	Mean [standard deviation] with usual care	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Mean MIDAS: change relative to baseline	**15.0 [24.0]**	**54.0 [14.0]**	**-39.00 (-46.70 to -31.30)**	**-2.0 (-2.5 to -1.5)**
Mean functionally incapacitating headache days per month	**3.0 [2.6]**	**4.6 [1.7]**	**-1.60 (-2.46 to -0.74)**	**-0.7 (-1.1 to -0.3)**

Bold - significant differences at 95% CI
CI – confidence interval

Appendix Table D119. Migraine cessation with specialized pharmaceutical care for migraine compared to standard counseling in adults (results from low risk of bias randomized controlled clinical trial)[200]

Definition of the outcome	Events/randomized with active intervention	Events/randomized with control intervention	Relative risk (95% CI)	Absolute risk difference (95% CI)
No headache during the preceding 4 weeks	21/201	16/209	1.4 (0.7to 2.5)	0.03 (-0.03 to 0.08)

CI – confidence interval

Appendix Table D120. Effectiveness of specialized pharmaceutical care for migraine compared to standard counseling for migraine prevention in adults (results from low risk of bias randomized controlled clinical trial)[200]

Definition of the outcome	Mean [standard deviation] with active intervention	Mean [standard deviation] with control intervention	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Days/month with headache	6.1 [6.7]	6.4 [6.9]	-0.30 (-1.61 to 1.01)	0.0 (-0.2 to 0.1)
Headache attacks/month	4.6 [6.1]	5.1 [7.3]	-0.43 (-1.74 to 0.88)	-0.1 (-0.3 to 0.1)
Intensity of pain: Untreated (on an analog scale of 1 (no headache) to 10 (extremely intense headache)	6.8 [3.4]	7.3 [2.9]	-0.46 (-1.07 to 0.15)	-0.1 (-0.3 to 0.0)
Intensity of pain: Treated (on an analog scale of 1 (no headache) to 10 (extremely intense headache)	3.3 [2.7]	3.5 [2.8]	-0.19 (-0.73 to 0.35)	-0.1 (-0.3 to 0.1)
Self-efficacy (Definitions of Schwarzer et al. Higher the score better the self-efficacy)	83.8 [7.5]	84.5 [8.2]	-0.78 (-2.30 to 0.74)	-0.1 (-0.3 to 0.1)
Quality of life: physical health (SF-36)	43.0 [10.3]	44.4 [9.1]	-1.37 (-3.25 to 0.51)	-0.1 (-0.3 to 0.1)
Quality of life: mental health (SF-36)	49.4 [9.1]	49.5 [10.4]	-0.09 (-1.98 to 1.80)	0.0 (-0.2 to 0.2)

Appendix Table D121. Effectiveness of intensive pharmaceutical care campaign for migraine prevention in adults (results from low risk of bias randomized controlled clinical trial)[199]

Definition of the outcome	Mean [standard deviation] with intensive pharmaceutical care campaign	Mean [standard deviation] with usual pharmacy service	Reported results
3 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	2.5 [Not reported]	2.5 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(2.45, 2.61), control=(2.29, 2.64)
3 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	7.1 [Not reported]	7.1 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(6.66,7.51), control=(6.49,7.65)
6 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	1.3 [Not reported]	1.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(1.21, 1.39), control=(1.19, 1.46)
6 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	5.3 [Not reported]	5.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(5.04, 5.61), control=(4.75, 5.89)
9 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	0.8 [Not reported]	0.8 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(0.73, 0.97), control=(0.78, 0.90)
9 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	4.2 [Not reported]	4.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(3.89, 4.51), control=(3.87, 4.72)
9 months: Prevalent users (One or more prescriptions 9 months before index date): <6 doses per month: Patients' triptan consumption (doses per month)	3.0 [Not reported]	3.0 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(2.78, 3.17), control=(2.71, 3.20)
9 months: Prevalent users (One or more prescriptions 9 months before index date): ≥6 and <15 doses per month: Patients' triptan consumption (doses per month)	9.9 [Not reported]	9.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(9.3, 10.5), control=(10.4, 11.2)
9 months: Prevalent users (One or more prescriptions 9 months before index date): ≥15 doses per month: Patients' triptan consumption (doses per month)	25.4 [Not reported]	26.0 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(20.9, 31.0), control=(22.4, 30.1)

Appendix Table D122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Botulinum toxin type A 25 U	Guyron, 2004[201] Non-RCT: Case report (unclear)	NR	NR	Depression of temple area (Patient reported)	28.3
Botulinum toxin type A 25 U	Guyron, 2004[201] Non-RCT: Case report (unclear)	NR	NR	Deformity (Physician examined)	100.0
Botulinum toxin type A (and Lidocaine 2 mL) 50 U	Omoigui, 2005[202] Non-RCT: Case report	NR	NR	Ptosis	100.0
Zonisamide Initiated with 25 mg/day and titrated up to 100 mg/day	Villani, 2011[203] Non-RCT: Uncontrolled prospective observational study	24	Migraine (I.H.S.)	Difficulty concentrating (transient)	5.9
Zonisamide Initiated with 25 mg/day and titrated up to 100 mg/day	Villani, 2011[203] Non-RCT: Uncontrolled prospective observational study	24	Migraine (I.H.S.)	Mood disorders (transient)	5.9
Zonisamide Initiated with 100 mg/day and titrated up to 300 mg/day	Ashkenazi, 2006[204] Non-RCT: Retrospective uncontrolled study (chart review)	Unclear	Episodic migraine or Transformed migraine according to the Silberstein-Lipton criteria	All	42.4
Zonisamide Initiated with 100 mg/day and titrated up to 300 mg/day	Ashkenazi, 2006[204] Non-RCT: Retrospective uncontrolled study (chart review)	Unclear	Episodic migraine or Transformed migraine according to the Silberstein-Lipton criteria	Fatigue	12.1
Lamotrigine 500 mg/die for I wk and 1000 mg/die for 24 wks	Pizza, 2011[205] Non-RCT: Uncontrolled study	25	NR	Somnolence, lack of concentration and a modest gastralgia	53.8
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	All	47.8
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Drowsiness	22.4
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Dizziness	5.9
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Slowness	11.9

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Constipation	5.9
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Ataxia	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Swollen face/body	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Weight gain	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (ICHD-2 criteria)	Discontinuation due to AE	22.4
Divalproex Mean: 974 mg /day	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Nausea	42.0
Divalproex Mean: 974 mg /day	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Infection	39.0
Divalproex Mean: 974 mg /day	Vukovic, 2009[206] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Alopecia	31.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Tremor	28.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Asthenia	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Dyspepsia	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Somnolence	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Pharyngitis	23.0

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Flu-like syndrome	21.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Pain	19.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Weight gain	19.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Abdominal pain	18.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Back pain	17.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Dizziness	17.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Diarrhea	16.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Rhinitis	15.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Nervousness	11.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Vomiting	11.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Insomnia	10.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Myalgia	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Sinusitis	9.0

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Depression	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Neck pain	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Bronchitis	8.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Increased appetite	8.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Accidental injury	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Allergic reaction	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Chest pain	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Increased cough	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Constipation	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Arthralgia	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Rash	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Ecchymosis	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[207] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Flatulence	6.0
Valproic acid 300 to 1200 mg per day	Kinze, 2001[208] Non-RCT: Prospective open-label	24	Migraine (International Headache Society)	Discontinuation due to hair loss	1.9

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Sleepiness	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Nausea	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Blurry vision	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Sluggish	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Libido	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	GI upset	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Confusion	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	All	50.0

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Nausea	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to GI Upset	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Confusion	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[209] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Sleepiness	6.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Discontinuation due to AE	12.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	3.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	50.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	5.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other	5.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	2.8
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	77.8
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	13.9
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other	8.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	3.3

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	33.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	10.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[210] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other	6.7
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Drowsiness, tiredness, weakness	13.7 vs. 20.5
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Dryness of mouth, sore tongue, bad taste	0.0 vs. 13.7
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Giddiness, ataxia	19.6 vs. 0.0
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Faintness, dizziness	5.9 vs. 6.8
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Nausea	11.8 vs. 6.8
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Increased appetite	2.0 vs. 0.0
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Epigastric discomfort	2.0 vs. 1.4
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Cramps, limb pains	3.9 vs. 1.4

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Irritability, agitation	3.9 vs. 2.7
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Insomnia, nightmare	2.0 vs. 1.4
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Bruising, prominent veins	0.0 vs. 1.4
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Skin itching, rash	3.9 vs. 0.0
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Blurred vision	3.9 vs. 0.0
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Lack of concentration	3.9 vs. 0.0
Carbamazepine 200 mg three times daily Vs. Clonidine 75 µg three times daily	Anthony, 1972[211] Non-RCT: Controlled trial	Variable (up to 72 for Clondine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Swelling of throat	2.0 vs. 0.0
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to AE	4.7
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Asthma (not previously experienced)	0.1
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Hypotension with or without bradycardia	2.5

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Excessive weight gain	0.8
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Congesitve heart failure	0.2
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Insomnia	0.7
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[212] Non-RCT: Prospective cohort	48	NR	Discontinuation due to Severe psychological depression	0.3
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Bradycardia	4.4
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Insomnia	1.5
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Depression	1.5
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Precordialgia	1.5 vs. 2.8
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Dizziness	2.9 vs. 0.0
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Paresthesia	0.0 vs. 8.3

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Gastralgia	0.0 vs. 5.6
Propranolol 40mg Vs. Metoprolol 40mg	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Bradycardia	4.4 vs. 16.7
Propranolol 40mg Vs. Metoprolol 40mg	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Hypotension	0.0 vs. 10.0
Propranolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to AE	11.8 vs. 16.7
Propranolol 40mg Vs. Metoprolol 40mg	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to AE	11.8 vs. 26.7
Metoprolol 40mg Vs. Methysergide 6 to 10 mg/day	Steardo, 1982[213] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to AE	26.7 vs. 16.7
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	All adverse effects	45.0
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	Discontinuation due to AE	10.0
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Angina pectoris	0.7
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Intermittent claudication	1.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Lower limb pains	2.6

Appendix Table 122. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, daily doses	Reference, design	Total length of followup	Migraine definition	Definition of the adverse effects (AE)	Rate ,%
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Upper limb pains	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Swelling of ankles	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): venules over nose and cheeks	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Facial flushing	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Vomiting	2.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Abdominal cramps	0.7
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Rash	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Scalp hair falling out	0.3
Methysergide 6 mg daily	Curran, 1964[214] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	NR	AE (Severe): Vertigo and ataxia	1.0
Ergotamine NR	Kim, 2005[215] Non-RCT: Case report	NA	NR	Upper extremity ischemia	100.0

NR- not reported

Appendix Table D123. Adverse effects with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Any adverse effect	6U 12 weeks	Saper, 2007[3] Low	8/45	3/11	0.7 (0.2 to 2.1)	2.35	-0.10 (-0.38 to 0.19)	3.06
Any adverse effect	7.5U 16 weeks	Elkind, 2006[6] Low	52/105	17/36	1.0 (0.7 to 1.6)	6.71	0.02 (-0.17 to 0.21)	4.58
Any adverse effect	9U 12 weeks	Saper, 2007[3] Low	11/49	3/12	0.9 (0.3 to 2.7)	2.48	-0.03 (-0.30 to 0.25)	3.25
Any adverse effect	10U 12 weeks	Saper, 2007[3] Low	9/44	3/11	0.8 (0.2 to 2.3)	2.42	-0.07 (-0.36 to 0.22)	3.02
Any adverse effect	25U 16 weeks	Elkind, 2006[6] Low	47/101	16/34	1.0 (0.7 to 1.5)	6.57	-0.01 (-0.20 to 0.19)	4.49
Any adverse effect	25U 12 weeks	Saper, 2007[3] Low	17/49	3/12	1.4 (0.5 to 4.0)	2.67	0.10 (-0.18 to 0.38)	3.15
Any adverse effect	50U 16 weeks	Elkind, 2006[6] Low	60/106	17/36	1.2 (0.8 to 1.8)	6.82	0.09 (-0.10 to 0.28)	4.59
Any adverse effect	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	97/174	13/59	2.5 (1.5 to 4.2)	5.86	0.34 (0.21 to 0.47)	5.77
Any adverse effect	80U 12 (one time injection) weeks	Petri, 2009[8] High	4/32	5/32	0.8 (0.2 to 2.7)	2.16	-0.03 (-0.20 to 0.14)	4.94
Any adverse effect	139 U 12 (one time injection) weeks	Cady, 2008[12] Low	0/40	0/19	2.6 (1.5 to 4.4)	5.68	0.00 (-0.08 to 0.08)	6.77
Any adverse effect	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	92/168	12/57	2.2 (1.6 to 3.0)	7.48	0.34 (0.21 to 0.47)	5.75
Any adverse effect	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005t[9] Low	88/173	42/182	2.2 (1.5 to 3.1)	7.12	0.28 (0.18 to 0.37)	6.41
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three	Aurora, 2010[1] Moderate	86/341	39/338	2.4 (1.8 to 3.3)	7.51	0.14 (0.08 to 0.19)	7.06

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
	injections: week 24, 36, 48) weeks							
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	116/347	49/358	1.3 (1.1 to 1.5)	8.56	0.20 (0.14 to 0.26)	7
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: wk 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	203/341	156/338	2.8 (2.1 to 3.8)	7.5	0.13 (0.06 to 0.21)	6.8
Any adverse effect	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	113/187	39/182	1.2 (1.0 to 1.3)	8.67	0.39 (0.30 to 0.48)	6.5
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	226/347	202/358	2.0 (0.9 to 4.7)	3.54	0.09 (0.02 to 0.16)	6.84
Any adverse effect	210U 12 (one time injection) weeks	Petri, 2009[8] High	12/32	6/32	3.1 (1.9 to 5.1)	5.89	0.19 (-0.03 to 0.40)	4.11
Any adverse effect	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	119/182	13/62	(Excluded) (0.0 to 0.0)		0.44 (0.32 to 0.57)	5.9
Any adverse effect	**All doses**	**Pooled**	**1360/2863**	**637/2168**	**1.6 (1.3 to 2.0)**	**100**	**0.16 (0.09 to 0.22)**	**100**
Back pain	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	3/174	0/59	2.4 (0.1 to 45.8)	17.6	0.02 (-0.01 to 0.05)	20.51
Back pain	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.3 (0.0 to 8.1)	15.48	-0.05 (-0.17 to 0.08)	1.28
Back pain	150 U 24 (three injection at day 0,	Silberstein, 2005[10] Low	4/168	0/57	3.1 (0.2 to 56.5)	18.12	0.02 (-0.01 to 0.06)	17.03

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
	day 90, and day 180) weeks							
Back pain	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	3/187	1/182	2.9 (0.3 to 27.8)	30.12	0.01 (-0.01 to 0.03)	44.76
Back pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	6/182	0/62	4.5 (0.3 to 78.3)	18.68	0.03 (0.00 to 0.07)	16.41
Back pain	All doses	Pooled	16/731	2/381	2.2 (0.6 to 7.7)	100	0.02 (0.00 to 0.03)	100
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	12/347	5/358	2.5 (0.9 to 7.0)	58.96	0.02 (0.00 to 0.04)	51.23
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	14/341	3/338	4.6 (1.3 to 16.0)	41.04	0.03 (0.01 to 0.06)	48.77
Discontinuations related to AE	All doses	Pooled	26/688	8/696	3.2 (1.4 to 7.1)	100	0.03 (0.01 to 0.04)	100
Dizziness	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.3 (0.0 to 8.1)	16.12	-0.05 (-0.17 to 0.08)	3.06
Dizziness	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	0/21	2.5 (0.1 to 49.9)	17.79	0.05 (-0.05 to 0.14)	5.31
Dizziness	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	1/173	3/182	0.4 (0.0 to 3.3)	31.37	-0.01 (-0.03 to 0.01)	43.71
Dizziness	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	4/187	0/182	8.8 (0.5 to 161.6)	18.76	0.02 (0.00 to 0.05)	41.31

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Dizziness	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	1/43	0/21	1.5 (0.1 to 35.3)	15.96	0.02 (-0.06 to 0.11)	6.61
Dizziness	All doses	Pooled	8/466	4/427	1.1 (0.3 to 4.1)	100	0.01 (-0.02 to 0.03)	100
Dysphagia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	3/174	0/59	2.4 (0.1 to 45.8)	23.99	0.02 (-0.01 to 0.05)	25.86
Dysphagia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	5/168	0/57	3.8 (0.2 to 67.2)	25.16	0.03 (-0.01 to 0.07)	19.36
Dysphagia	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	4/173	0/182	9.5 (0.5 to 174.5)	24.56	0.02 (0.00 to 0.05)	40.45
Dysphagia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	11/182	0/62	7.8 (0.5 to 130.3)	26.29	0.06 (0.02 to 0.10)	14.33
Dysphagia	**All doses**	**Pooled**	**23/697**	**1/360**	**5.1 (1.2 to 21.8)**	**100**	**0.03 (0.01 to 0.04)**	**100**
Eyelid edema	7.5U 16 weeks	Elkind, 2006[6] Low	1/105	0/36	1.0 (0.0 to 25.1)	18.17	0.01 (-0.03 to 0.05)	21.56
Eyelid edema	25U 16 weeks	Elkind, 2006[6] Low	0/101	0/34	5.2 (0.3 to 88.6)	20.8	0.00 (-0.04 to 0.04)	22.27
Eyelid edema	50U 16 weeks	Elkind, 2006[6] Low	7/106	0/36	0.5 (0.0 to 7.8)	21.78	0.07 (0.01 to 0.13)	15.8
Eyelid edema	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	1/43	1/21	24.3 (1.5 to 408.0)	20.96	-0.02 (-0.12 to 0.08)	8.51
Eyelid edema	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	12/187	0/182	0.2 (0.0 to 4.1)	18.3	0.06 (0.03 to 0.10)	24.28
Eyelid edema	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	(Excluded) (0.0 to 0.0)		-0.05 (-0.15 to 0.06)	7.59
Eyelid edema	All doses	Pooled	21/585	1/330	1.7 (0.3 to 9.7)	100	0.02 (-0.01 to 0.06)	100

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Headache	6U 12 weeks	Saper, 2007[3] Low	2/45	0/11	1.2 (0.1 to 23.2)	1.84	0.04 (-0.10 to 0.18)	1.94
Headache	7.5U 16 weeks	Elkind, 2006[6] Low	1/105	1/36	0.3 (0.0 to 5.3)	2.15	-0.02 (-0.08 to 0.04)	11.71
Headache	9U 12 weeks	Saper, 2007[3] Low	0/49	1/12	0.1 (0.0 to 2.0)	1.64	-0.08 (-0.26 to 0.09)	1.22
Headache	10U 12 weeks	Saper, 2007[3] Low	1/44	0/11	0.8 (0.0 to 18.4)	1.64	0.02 (-0.10 to 0.15)	2.43
Headache	25U 12 weeks	Saper, 2007[3] Low	3/49	1/12	0.7 (0.1 to 6.5)	3.42	-0.02 (-0.19 to 0.15)	1.31
Headache	25U 16 weeks	Elkind, 2006[6] Low	2/101	1/34	0.7 (0.1 to 7.4)	2.88	-0.01 (-0.07 to 0.05)	9.99
Headache	50U 16 weeks	Elkind, 2006[6] Low	8/106	1/36	2.7 (0.4 to 21.0)	3.87	0.05 (-0.03 to 0.12)	6.99
Headache	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	7/174	3/59	0.8 (0.2 to 3.0)	9.29	-0.01 (-0.07 to 0.05)	9.46
Headache	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.1)	1.62	-0.05 (-0.15 to 0.06)	3.39
Headache	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/168	3/57	1.6 (0.5 to 5.4)	11.04	0.03 (-0.04 to 0.10)	7.57
Headache	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	12/173	11/182	1.1 (0.5 to 2.5)	25.84	0.01 (-0.04 to 0.06)	14.36
Headache	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	11/187	9/182	1.2 (0.5 to 2.8)	22.03	0.01 (-0.04 to 0.06)	17.75
Headache	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	15/182	3/62	1.7 (0.5 to 5.7)	11.13	0.03 (-0.03 to 0.10)	8.5

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Headache	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.1)	1.62	-0.05 (-0.15 to 0.06)	3.39
Headache	All doses	Pooled	76/1469	33/735	1.1 (0.7 to 1.6)	100	0.01 (-0.02 to 0.02)	100
Hypertonia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	13/174	0/59	9.3 (0.6 to 153.4)	8	0.08 (0.03 to 0.12)	17.89
Hypertonia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	15/168	0/57	10.6 (0.6 to 175.0)	8.04	0.09 (0.04 to 0.14)	15.31
Hypertonia	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	9/173	4/182	2.4 (0.7 to 7.5)	46.94	0.03 (-0.01 to 0.07)	23.81
Hypertonia	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	13/187	2/182	6.3 (1.4 to 27.6)	29.01	0.06 (0.02 to 0.10)	23.67
Hypertonia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Risk of bias Low	13/182	0/62	9.1 (0.6 to 151.6)	8	0.07 (0.03 to 0.12)	19.32
Hypertonia	All doses	Pooled	63/884	7/542	4.4 (2.0 to 9.8)	100	0.06 (0.04 to 0.08)	100
Neck pain	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	30/174	1/59	10.2 (1.4 to 73.0)	12.65	0.16 (0.09 to 0.22)	12.91
Neck pain	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	1/21	1.0 (0.1 to 10.7)	10.24	0.00 (-0.11 to 0.11)	9.63
Neck pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	37/168	1/57	12.6 (1.8 to 89.4)	12.7	0.20 (0.13 to 0.27)	12.42
Neck pain	105U-260U (“Follow-the-pain” approach) 24 (three	Mathew, 2005[9] Low	23/173	1/182	24.2 (3.3 to 177.2)	12.5	0.13 (0.08 to 0.18)	13.93

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
	injections at day 0, day 90, and day 180) weeks							
Neck pain	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	20/341	0/338	40.6 (2.5 to 669.2)	8.02	0.06 (0.03 to 0.08)	15.51
Neck pain	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	32/187	8/182	3.9 (1.8 to 8.2)	24.5	0.13 (0.07 to 0.19)	13.18
Neck pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	41/182	1/62	14.0 (2.0 to 99.4)	12.7	0.21 (0.14 to 0.28)	12.66
Neck pain	240U 12 (one time injection)weeks	Chankrachang, 2011[7] Risk of bias Low	0/43	1/21	0.2 (0.0 to 4.1)	6.7	-0.05 (-0.15 to 0.06)	9.76
Neck pain	**All doses**	**Pooled**	**185/1311**	**13/922**	**6.4 (2.5 to 16.4)**	**100**	**0.11 (0.06 to 0.16)**	**100**
Neck rigidity	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/174	0/59	9.9 (0.6 to 164.1)	5.8	0.08 (0.03 to 0.13)	18.99
Neck stiffness	100U 16 weeks	Freitag, 2008[4] Low	1/20	1/21	1.1 (0.1 to 15.7)	6.24	0.00 (-0.13 to 0.13)	5.5
Neck rigidity	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/168	0/57	10.0 (0.6 to 164.2)	5.8	0.08 (0.04 to 0.13)	18.54
Neck rigidity	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	8/173	2/182	4.2 (0.9 to 19.5)	19.34	0.04 (0.00 to 0.07)	22.59
Neck rigidity	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	19/187	6/182	3.1 (1.3 to 7.5)	56.93	0.07 (0.02 to 0.12)	17.98

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Neck rigidity	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	27/182	0/62	18.6 (1.2 to 301.0)	5.89	0.15 (0.09 to 0.21)	16.4
Neck rigidity	**All doses**	**Pooled**	**83/904**	**10/563**	**3.9 (2.0 to 7.7)**	**100**	**0.08 (0.04 to 0.11)**	**100**
Injection site pain	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	8/174	3/59	0.9 (0.2 to 3.3)	17.11	-0.01 (-0.07 to 0.06)	3.24
Injection site pain	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.3 (0.0 to 8.1)	2.87	-0.05 (-0.17 to 0.08)	1.19
Injection site pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	10/168	3/57	0.2 (0.0 to 4.1)	18.19	-0.05 (-0.15 to 0.06)	2.87
Injection site pain	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	4/173	4/182	1.1 (0.3 to 4.0)	15.26	0.01 (-0.06 to 0.08)	13.95
Injection site pain	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	4/187	1/182	1.1 (0.3 to 4.1)	6.02	0.00 (-0.03 to 0.03)	24.43
Injection site pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	17/182	3/62	3.9 (0.4 to 34.5)	20.14	0.02 (-0.01 to 0.04)	2.82
Injection site pain	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	6.8 (0.4 to 131.0)	2.87	0.02 (-0.01 to 0.04)	1.19
Pain	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	3/187	0/182	1.1 (0.2 to 5.1)	3.28	0.00 (-0.03 to 0.03)	30.95
Pain	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	3/173	3/182	1.9 (0.6 to 6.3)	11.38	0.04 (-0.03 to 0.11)	18.49

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Pain	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.2 (0.0 to 4.1)	2.9	-0.05 (-0.15 to 0.06)	0.87
Pain	All doses	Pooled	49/1350	20/969	1.2 (0.7 to 2.0)	100	0.01 (0.00 to 0.02)	100
Blepharoptosis	6U 12 weeks	Saper, 2007[3] Low	1/45	0/11	0.8 (0.0 to 18.0)	3.72	0.02 (-0.10 to 0.15)	2.32
Blepharoptosis	7.5U 16 weeks	Elkind, 2006[6] Low	2/105	0/36	1.7 (0.1 to 35.5)	4.03	0.02 (-0.03 to 0.07)	8.98
Blepharoptosis	9U 12 weeks	Saper, 2007[3] Low	0/49	0/12	2.2 (0.1 to 37.5)	4.5	0.00 (-0.12 to 0.12)	2.59
Blepharoptosis	10U 12 weeks	Saper, 2007[3] Low	0/44	0/11	3.8 (0.2 to 66.5)	4.45	0.00 (-0.12 to 0.12)	2.56
Blepharoptosis	25U 12 weeks	Saper, 2007[3] Low	4/49	0/12	6.7 (0.4 to 112.7)	4.57	0.08 (-0.06 to 0.22)	1.92
Blepharoptosis	25U 16 weeks	Elkind, 2006[6] Low	5/101	0/34	5.9 (0.3 to 99.4)	4.58	0.05 (-0.01 to 0.11)	7.06
Blepharoptosis	25U 12 weeks	Silberstein, 2000[5] Moderate	6/42	0/21	7.7 (0.5 to 128.1)	4.62	0.14 (0.02 to 0.27)	2.33
Blepharoptosis	50U 16 weeks	Elkind, 2006[6] Low	8/106	0/36	2.0 (0.3 to 16.6)	8.33	0.08 (0.01 to 0.14)	6.46
Blepharoptosis	75U 12 weeks	Silberstein, 2000[5] Risk of bias Moderate	7/40	0/20	4.9 (0.2 to 100.5)	8.52	0.18 (0.04 to 0.31)	2
Blepharoptosis	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	6/174	1/59	2.4 (0.3 to 18.9)	8.89	0.02 (-0.03 to 0.06)	9.83
Blepharoptosis	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	0/21	12.6 (1.7 to 96.1)	26.7	0.00 (-0.07 to 0.07)	5.7
Blepharoptosis	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	7/168	1/57	9.4 (2.9 to 30.3)	8.98	0.03 (-0.02 to 0.08)	9.27
Blepharoptosis	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	12/173	1/182	4.1 (0.5 to 30.8)	4.09	0.02 (-0.02 to 0.07)	10.51

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Blepharoptosis	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	29/187	3/182	2.5 (0.1 to 49.9)	4.02	0.06 (0.03 to 0.10)	7.63
Blepharoptosis	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	12/182	1/62	(Excluded) (0.0 to 0.0)		0.14 (0.08 to 0.19)	8.85
Blepharoptosis	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	0/21	(Excluded) (0.0 to 0.0)		0.05 (0.00 to 0.10)	3.77
Blepharoptosis	210U plus 80U 12 (one time injection) weeks	Petri, 2009[8] High	2/64	0/63	(Excluded) (0.0 to 0.0)		0.05 (-0.05 to 0.14)	8.21
Blepharoptosis	**All doses**	**Pooled**	**103/1615**	**7/839**	**4.7 (2.6 to 8.7)**	**5.58**	**0.05 (0.03 to 0.07)**	**100**
Muscle weakness	6U 12 weeks	Saper, 2007[3] Low	0/45	0/11	3.4 (0.2 to 56.2)	16.37	0.00 (-0.12 to 0.12)	10.02
Muscle weakness	9U 12 weeks	Saper, 2007[3] Low	0/49	0/12	20.2 (1.3 to 326.0)	16.74	0.00 (-0.11 to 0.11)	10.37
Muscle weakness	10U 12 weeks	Saper, 2007[3] Low	0/44	0/11	30.5 (1.9 to 488.1)	16.84	0.00 (-0.12 to 0.12)	10.01
Muscle weakness	25U 12 weeks	Saper, 2007[3] R Low	6/49	0/12	81.0 (5.0 to 1308.0)	16.71	0.12 (-0.02 to 0.26)	9.1
Muscle weakness	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	29/174	0/59	40.6 (2.5 to 669.2)	16.48	0.17 (0.11 to 0.23)	12.09
Muscle weakness	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	44/168	0/57	38.3 (2.4 to 610.4)	16.87	0.26 (0.19 to 0.33)	11.76
Muscle weakness	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	38/173	0/182	(Excluded) (0.0 to 0.0)		0.22 (0.16 to 0.28)	12.03
Muscle weakness	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course:	Aurora, 2010[1] Moderate	20/341	0/338	(Excluded) (0.0 to 0.0)		0.06 (0.03 to 0.08)	12.87

Appendix Table 123. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse effect	Dose Weeks of treatment	Reference Risk of bias	Events randomized botox	Events randomized placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
	week 1, week 12; open label three injections: week 24, 36, 48) weeks							
Muscle weakness	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	56/182	0/62	(Excluded) (0.0 to 0.0)		0.31 (0.24 to 0.38)	11.76
Muscle weakness	**All doses**	**Pooled**	**193/1225**	**1/743**	**25.5 (8.2 to 79.5)**	**100**	**0.13 (0.06 to 0.21)**	**100**
Fever	100U 16 weeks	Freitag, 2008[4] Low	0/20	2/21	1.3 (0.4 to 4.3)	5.48	0.02 (-0.09 to 0.13)	9.11
Flu syndrome	25U 16 weeks	Elkind, 2006[6] Low	4/101	3/34	0.4 (0.1 to 1.9)	23.26	-0.05 (-0.15 to 0.05)	18.89
Flu syndrome	50U 16 weeks	Elkind, 2006[6] Low	7/106	3/36	0.8 (0.2 to 2.9)	28.82	-0.02 (-0.12 to 0.09)	19.16
Flu syndrome	7.5U 16 weeks	Elkind, 2006[6] Low	11/105	3/36	0.2 (0.0 to 4.1)	32.7	-0.10 (-0.24 to 0.05)	17.18
Pyrexia	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.1)	4.87	-0.05 (-0.15 to 0.06)	17.83
Pyrexia	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.1)	4.87	-0.05 (-0.15 to 0.06)	17.83
Pyrexia	All doses	Pooled	22/418	12/169	0.6 (0.3 to 1.3)	100	-0.03 (-0.08 to 0.01)	100

CI – confidence interval

Appendix Table D124. Adverse effects with botox vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Any adverse effect	6U 12 weeks	Saper, 2007[3] Low	8/45	3/11	0.6 (0.1 to 2.7)	0.027	0.04 (-0.16 to 0.24)	0.03
Any adverse effect	7.5U 16 weeks	Elkind, 2006[6] Low	52/105	17/36	1.1 (0.5 to 2.3)	0.058	0.07 (-0.09 to 0.22)	0.045
Any adverse effect	9U 12 weeks	Saper, 2007[3] Low	11/49	3/12	0.9 (0.2 to 3.8)	0.029	0.07 (-0.13 to 0.26)	0.031
Any adverse effect	10U 12 weeks	Saper, 2007[3] Low	9/44	3/11	6.2 (0.3 to 114.2)	0.009	0.19 (0.05 to 0.33)	0.049
Any adverse effect	25U 16 weeks	Elkind, 2006[6] Low	47/101	16/34	1.0 (0.4 to 2.1)	0.056	0.05 (-0.11 to 0.21)	0.044
Any adverse effect	25U 12 weeks	Saper, 2007[3] Low	17/49	3/12	1.6 (0.4 to 6.7)	0.03	0.13 (-0.07 to 0.32)	0.03
Any adverse effect	50U 16 weeks	Elkind, 2006[6] Low	60/106	17/36	1.5 (0.7 to 3.1)	0.058	0.11 (-0.04 to 0.27)	0.045
Any adverse effect	75 U 24 weeks	Silberstein, 2005[10] Low	97/174	13/59	4.5 (2.2 to 8.8)	0.062	0.30 (0.19 to 0.42)	0.057
Any adverse effect	80U 12 weeks	Petri, 2009[8] High	4/32	5/32	0.8 (0.2 to 3.2)	0.03	0.02 (-0.12 to 0.17)	0.048
Any adverse effect	139U 12 weeks	Cady, 2008[12] Low	0/40	0/19	0.5 (0.0 to 25.2)	0.005	0.01 (-0.06 to 0.09)	0.067
Any adverse effect	150 U 24 weeks	Silberstein, 2005[10] Low	92/168	12/57	4.5 (2.2 to 9.2)	0.061	0.30 (0.19 to 0.42)	0.056
Any adverse effect	105U-260U (“Follow-the-pain” approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Risk of biasLow	88/173	42/182	3.5 (2.2 to 5.4)	0.075	0.26 (0.17 to 0.36)	0.063
Any adverse effect	155U-195U [Follow-the-pain strategy] 24 (two injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	86/341	39/338	2.6 (1.7 to 3.9)	0.078	0.14 (0.08 to 0.19)	0.07

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	116/347	49/358	3.2 (2.2 to 4.6)	0.08	0.20 (0.14 to 0.26)	0.069
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (2 injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	203/341	156/338	1.7 (1.3 to 2.3)	0.083	0.14 (0.06 to 0.21)	0.067
Any adverse effect	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	113/187	39/182	5.6 (3.5 to 8.9)	0.075	0.37 (0.28 to 0.45)	0.064
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (3 injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	226/347	202/358	1.4 (1.1 to 2.0)	0.083	0.09 (0.02 to 0.16)	0.068
Any adverse effect	210U 12 (one time injection) weeks	Petri, 2009[8] High	12/32	6/32	2.6 (0.8 to 8.1)	0.039	0.18 (0.01 to 0.35)	0.04
Any adverse effect	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	119/182	13/62	7.1 (3.6 to 14.1)	0.062	0.40 (0.28 to 0.51)	0.058
Any adverse effect	**Pooled**		**1360/2863**	**637/2168**	**2.2 (1.5 to 3.0)**	**1**	**0.16 (0.09 to 0.23)**	**1**
Back pain	75 U 24 (3 injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	3/174	0/59	2.4 (0.1 to 47.7)	0.177	0.02 (-0.01 to 0.04)	0.205

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Back pain	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.148	0.01 (-0.02 to 0.04)	0.013
Back pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	4/168	0/57	3.1 (0.2 to 59.3)	0.182	0.02 (0.00 to 0.04)	0.17
Back pain	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	3/187	1/182	3.0 (0.3 to 28.6)	0.304	0.01 (-0.01 to 0.03)	0.448
Back pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	6/182	0/62	4.6 (0.3 to 82.9)	0.188	0.02 (0.00 to 0.05)	0.164
Back pain	**All doses**	**Pooled**	**16/731**	**2/381**	**4.9 (1.2 to 35.7)**		**0.02 (0.00 to 0.04)**	
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	12/347	5/358	2.5 (0.9 to 7.3)	0.587	0.03 (0.01 to 0.04)	0.512
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (2 injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	14/341	3/338	4.8 (1.4 to 16.8)	0.413	0.03 (0.02 to 0.04)	0.488
Discontinua-tions related to AE	**All doses**	**Pooled**	**26/688**	**8/696**	**3.5 (1.2 to 10.9)**	**1**	**0.03 (0.01 to 0.05)**	**1**
Dizziness	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.156	0.00 (-0.05 to 0.05)	0.031
Dizziness	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	0/21	2.6 (0.1 to 56.4)	0.174	0.02 (-0.03 to 0.06)	0.053

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Dizziness	105U-260U ("Follow-the-pain" approach) 24 weeks	Mathew, 2005[9] Low	1/173	3/182	0.3 (0.0 to 3.4)	0.32	-0.01 (-0.03 to 0.01)	0.437
Dizziness	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	4/187	0/182	9.0 (0.5 to 167.5)	0.193	0.02 (0.00 to 0.04)	0.413
Dizziness	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	1/43	0/21	1.5 (0.1 to 38.8)	0.157	0.01 (-0.03 to 0.06)	0.066
Dizziness	All doses	Pooled	8/466	4/427	1.8 (0.5 to 8.0)	1	0.01 (-0.02 to 0.04)	1
Dysphagia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	3/174	0/59	2.4 (0.1 to 47.7)	0.24	0.03 (0.00 to 0.05)	0.258
Dysphagia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	5/168	0/57	3.9 (0.2 to 71.1)	0.251	0.03 (0.01 to 0.05)	0.193
Dysphagia	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 205[9] Low	4/173	0/182	9.7 (0.5 to 181.3)	0.248	0.03 (0.01 to 0.05)	0.404
Dysphagia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	11/182	0/62	8.4 (0.5 to 144.4)	0.262	0.04 (0.02 to 0.07)	0.144
Dysphagia	**All doses**	**Pooled**	**23/697**	**1/360**			**0.03 (0.01 to 0.05)**	**1**
Eyelid edema	7.5U 16 weeks	Elkind, 2006[6] Low	1/105	0/36	1.0 (0.0 to 26.3)	0.16	0.01 (-0.03 to 0.05)	0.217
Eyelid edema	25U 16 weeks	Elkind, 2006[6] Low	0/101	0/34	0.3 (0.0 to 17.5)	0.121	0.00 (-0.03 to 0.04)	0.225
Eyelid edema	50U 16 weeks	Elkind, 2006[6] Low	7/106	0/36	5.5 (0.3 to 98.8)	0.184	0.05 (0.00 to 0.09)	0.16
Eyelid edema	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	1/43	1/21	0.5 (0.0 to 8.0)	0.189	0.00 (-0.06 to 0.06)	0.081

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Eyelid edema	110 U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	12/187	0/182	26.0 (1.5 to 442.4)	0.188	0.06 (0.02 to 0.09)	0.245
Eyelid edema	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.159	0.00 (-0.06 to 0.06)	0.072
Eyelid edema	All doses	Pooled	21/585	1/330	5.5 (0.8 to 62.0)	1	0.02 (-0.02 to 0.06)	1
Headache	6U 12 weeks	Saper, 2007[3] Low	2/45	0/11	1.3 (0.1 to 29.5)	0.019	0.01 (-0.05 to 0.06)	0.022
Headache	7.5U 16 weeks	Elkind, 2006[6] Low	1/105	1/36	0.3 (0.0 to 5.5)	0.023	-0.01 (-0.05 to 0.03)	0.118
Headache	9U 12 weeks	Saper, 2007[3] Low	0/49	1/12	0.1 (0.0 to 2.0)	0.017	-0.01 (-0.07 to 0.05)	0.012
Headache	10U 12 weeks	Saper, 2007[3] Low	1/44	0/11	0.8 (0.0 to 20.8)	0.017	0.00 (-0.05 to 0.06)	0.025
Headache	25U 12 weeks	Saper, 2007[3] Low	3/49	1/12	0.7 (0.1 to 7.6)	0.032	0.00 (-0.06 to 0.06)	0.013
Headache	25U 16 weeks	Elkind, 2006[6] Low	2/101	1/34	0.7 (0.1 to 7.6)	0.031	-0.01 (-0.05 to 0.04)	0.096
Headache	50U 16 weeks	Elkind, 2006[6] Low	8/106	1/36	2.9 (0.3 to 23.7)	0.04	0.02 (-0.03 to 0.07)	0.07
Headache	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	7/174	3/59	0.8 (0.2 to 3.1)	0.094	-0.01 (-0.05 to 0.04)	0.095
Headache	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.017	-0.01 (-0.07 to 0.04)	0.032
Headache	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/168	3/57	1.6 (0.5 to 5.9)	0.109	0.01 (-0.03 to 0.06)	0.075
Headache	105U-260U (“Follow-the-pain” approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	12/173	11/182	1.2 (0.5 to 2.7)	0.252	0.01 (-0.03 to 0.05)	0.145

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Headache	110U to 260 U per treatment weeks	Aurora, 2007[14] Moderate	11/187	9/182	1.2 (0.5 to 3.0)	0.22	0.01 (-0.03 to 0.04)	0.179
Headache	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	15/182	3/62	1.8 (0.5 to 6.3)	0.111	0.02 (-0.03 to 0.06)	0.086
Headache	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.017	-0.01 (-0.07 to 0.04)	0.032
Headache	All doses	Pooled	76/1469	33/735	1.0 (0.5 to 1.6)	1	0.00 (-0.02 to 0.03)	1
Hypertonia	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	13/174	0/59	9.9 (0.6 to 170.0)	0.082	0.07 (0.04 to 0.10)	0.179
Hypertonia	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	15/168	0/57	11.6 (0.7 to 197.3)	0.082	0.07 (0.04 to 0.10)	0.153
Hypertonia	105U-260U (“Follow-the-pain” approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	9/173	4/182	2.4 (0.7 to 8.1)	0.461	0.05 (0.02 to 0.08)	0.238
Hypertonia	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	13/187	2/182	6.7 (1.5 to 30.2)	0.292	0.06 (0.04 to 0.09)	0.236
Hypertonia	22U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	13/182	0/62	10.0 (0.6 to 170.0)	0.082	0.07 (0.04 to 0.10)	0.194
Hypertonia	**All doses**	**Pooled**	**63/884**	**7/542**	**7.3 (3.1 to 20.9)**	**1**	**0.06 (0.04 to 0.09)**	**1**
Neck pain	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	30/174	1/59	12.1 (1.6 to 90.7)	0.128	0.15 (0.09 to 0.21)	0.13
Neck pain	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	1/21	1.0 (0.1 to 11.4)	0.101	0.04 (-0.05 to 0.13)	0.094

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Neck pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	37/168	1/57	15.8 (2.1 to 118.1)	0.128	0.19 (0.12 to 0.25)	0.125
Neck pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	23/173	1/182	27.8 (3.7 to 207.9)	0.128	0.13 (0.08 to 0.17)	0.14
Neck pain	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	20/341	0/338	43.2 (2.6 to 716.7)	0.085	0.06 (0.04 to 0.09)	0.156
Neck pain	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	32/187	8/182	4.5 (2.0 to 10.0)	0.233	0.13 (0.07 to 0.18)	0.133
Neck pain	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	41/182	1/62	17.7 (2.4 to 131.9)	0.128	0.19 (0.13 to 0.26)	0.127
Neck pain	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.069	0.01 (-0.08 to 0.10)	0.095
Neck pain	**All doses**	**Pooled**	**185/1311**	**13/922**	**9.5 (4.7 to 19.2)**	**1**	**0.11 (0.05 to 0.17)**	**1**
Neck rigidity	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/174	0/59	10.8 (0.6 to 183.1)	0.061	0.08 (0.04 to 0.12)	0.19
Neck stiffness	100U 16 weeks	Freitag, 2008[4] Low	1/20	1/21	1.1 (0.1 to 18.1)	0.061	0.06 (-0.01 to 0.12)	0.055
Neck rigidity	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	14/168	0/57	10.8 (0.6 to 183.9)	0.061	0.08 (0.04 to 0.12)	0.185

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Neck rigidity	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	8/173	2/182	4.4 (0.9 to 20.8)	0.201	0.04 (0.01 to 0.07)	0.226
Neck rigidity	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	19/187	6/182	3.3 (1.3 to 8.5)	0.554	0.07 (0.03 to 0.11)	0.18
Neck rigidity	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	27/182	0/62	22.1 (1.3 to 368.0)	0.062	0.12 (0.08 to 0.17)	0.164
Neck rigidity	**All doses**	**Pooled**	**83/904**	**10/563**	**6.2 (2.9 to 14.1)**	**1**	**0.08 (0.04 to 0.11)**	**1**
Injection site pain	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	8/174	3/59	0.9 (0.2 to 3.5)	0.167	0.00 (-0.04 to 0.04)	0.032
Injection site pain	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.029	-0.01 (-0.05 to 0.04)	0.011
Injection site pain	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	10/168	3/57	1.1 (0.3 to 4.3)	0.176	0.00 (-0.04 to 0.04)	0.029
Injection site pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	4/173	4/182	1.1 (0.3 to 4.3)	0.157	0.00 (-0.03 to 0.03)	0.14
Injection site pain	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	4/187	1/182	4.0 (0.4 to 35.7)	0.064	0.01 (-0.01 to 0.03)	0.245
Injection site pain	225U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 205[10] Low	17/182	3/62	2.0 (0.6 to 7.2)	0.194	0.01 (-0.03 to 0.05)	0.029
Injection site pain	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.029	-0.01 (-0.05 to 0.04)	0.011

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Pain	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	3/187	0/182	6.9 (0.4 to 135.0)	0.035	0.01 (-0.01 to 0.03)	0.31
Pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	3/173	3/182	1.1 (0.2 to 5.3)	0.119	0.00 (-0.02 to 0.02)	0.185
Pain	100U 16 weeks	Freitag, 2008[4] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.029	-0.01 (-0.05 to 0.04)	0.009
Injection site pain	**All doses**	**Pooled**	**49/1350**	**20/969**	**1.4 (0.7 to 2.5)**	**1**	**0.00 (-0.02 to 0.02)**	**1**
Blepharoptosis	6U 12 weeks	Saper, 2007[3] Low	1/45	0/11	0.8 (0.0 to 20.3)	0.034	0.04 (-0.03 to 0.11)	0.023
Blepharoptosis	7.5U 16 weeks	Elkind, 2006[6] Low	2/105	0/36	1.8 (0.1 to 37.6)	0.038	0.03 (-0.01 to 0.07)	0.089
Blepharoptosis	9U 12 weeks	Saper, 2007[3] Low	0/49	0/12	0.3 (0.0 to 13.4)	0.023	0.03 (-0.03 to 0.10)	0.029
Blepharoptosis	10U 12 weeks	Saper, 2007[3] Low	0/44	0/11	0.3 (0.0 to 13.7)	0.023	0.04 (-0.03 to 0.10)	0.026
Blepharoptosis	25U 12 weeks	Saper, 2007[3] Low	4/49	0/12	2.5 (0.1 to 49.1)	0.04	0.06 (-0.01 to 0.13)	0.021
Blepharoptosis	25U 16 weeks	Elkind, 2006[6] Low	5/101	0/34	3.9 (0.2 to 73.0)	0.042	0.05 (0.00 to 0.10)	0.07
Blepharoptosis	25U 12 weeks	Silberstein, 2000[5] Moderate	6/42	0/21	7.7 (0.4 to 142.8)	0.042	0.08 (0.01 to 0.15)	0.023
Blepharoptosis	50U 16 weeks	Elkind, 2006[6] Low	8/106	0/36	6.3 (0.4 to 111.9)	0.043	0.07 (0.02 to 0.12)	0.064
Blepharoptosis	75U 12 weeks	Silberstein, 2000[5] Moderate	7/40	0/20	9.2 (0.5 to 169.4)	0.042	0.09 (0.02 to 0.16)	0.02
Blepharoptosis	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	6/174	1/59	2.1 (0.2 to 17.6)	0.078	0.03 (-0.01 to 0.06)	0.098
Blepharoptosis	120U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	0/21	0.5 (0.0 to 25.8)	0.023	0.02 (-0.03 to 0.08)	0.057
Blepharoptosis	150U 24 (three injection at day 0,	Silberstein, 2005[10] Low	7/168	1/57	2.4 (0.3 to 20.2)	0.08	0.03 (-0.01 to 0.07)	0.092

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
	day 90, and day 180) weeks							
Blepharoptosis	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	12/173	1/182	13.5 (1.7 to 104.9)	0.085	0.06 (0.03 to 0.10)	0.104
Blepharoptosis	110U to 260U per treatment weeks	Aurora, 2007[14] Moderate	29/187	3/182	11.0 (3.3 to 36.6)	0.246	0.11 (0.07 to 0.16)	0.076
Blepharoptosis	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	12/182	1/62	4.3 (0.5 to 33.8)	0.084	0.05 (0.01 to 0.09)	0.088
Blepharoptosis	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	2/43	0/21	2.6 (0.1 to 56.4)	0.038	0.05 (-0.01 to 0.11)	0.038
Blepharoptosis	210U plus 80U 12 (one time injection) weeks	Petri, 2009[8] High	2/64	0/63	5.1 (0.2 to 108.0)	0.038	0.04 (-0.01 to 0.08)	0.082
Blepharoptosis	**All doses**	**Pooled**	**103/1615**	**7/839**	**8.0 (3.5 to 21.6)**	**1**	**0.05 (0.03 to 0.08)**	**1**
Muscle weakness	6U 12 weeks	Saper, 2007[3] Low	0/45	0/11	0.3 (0.0 to 13.4)	0.087	0.03 (-0.07 to 0.13)	0.1
Muscle weakness	9U 12 weeks	Saper, 2007[3] Low	0/49	0/12	0.3 (0.0 to 13.4)	0.087	0.03 (-0.07 to 0.12)	0.104
Muscle weakness	10U 12 weeks	Saper, 2007[3] Low	0/44	0/11	0.3 (0.0 to 13.7)	0.087	0.03 (-0.07 to 0.13)	0.1
Muscle weakness	25U 12 weeks	Saper, 2007[3] Low	6/49	0/12	3.7 (0.2 to 71.0)	0.119	0.13 (0.01 to 0.24)	0.091
Muscle weakness	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	29/174	0/59	24.1 (1.5 to 401.3)	0.124	0.16 (0.11 to 0.22)	0.121
Muscle weakness	150 U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	44/168	0/57	41.1 (2.5 to 679.2)	0.124	0.25 (0.18 to 0.32)	0.118

Appendix Table 124. Adverse effects with botox versus placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse effect	Dose and weeks of treatment	Reference Risk of bias	Events/ randomized with botox	Events/ randomized with placebo	Bayesian odds ratio (median, 24 and 95% CI)	Weight	Absolute risk difference, maximum likelihood method (95% CI)	Weight
Muscle weakness	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[9] Low	38/173	0/182	103.7 (6.3 to 1703.1)	0.124	0.21 (0.15 to 0.27)	0.12
Muscle weakness	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Moderate	20/341	0/338	43.2 (2.6 to 716.7)	0.124	0.06 (0.03 to 0.09)	0.129
Muscle weakness	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[10] Low	56/182	0/62	55.8 (3.4 to 918.6)	0.124	0.29 (0.22 to 0.36)	0.118
Muscle weakness	**All doses**	**Pooled**	**193/1225**	**1/743**			**0.13 (0.06 to 0.21)**	**1**
Fever	100U 16 weeks	Freitag, 2008[4] Low	0/20	2/21	0.2 (0.0 to 4.2)	0.059	-0.05 (-0.11 to 0.01)	0.094
Flu syndrome	25U 16 weeks	Elkind, 2006[6] Low	4/101	3/34	0.4 (0.1 to 2.0)	0.234	-0.04 (-0.10 to 0.01)	0.194
Flu syndrome	50U 16 weeks	Elkind, 2006[6] Low	7/106	3/36	0.8 (0.2 to 3.2)	0.284	-0.03 (-0.09 to 0.02)	0.197
Flu syndrome	7.5U 16 weeks	Elkind, 2006[6] Low	11/105	3/36	1.3 (0.3 to 4.9)	0.316	-0.02 (-0.08 to 0.04)	0.177
Pyrexia	240U 12 (one time injection) weeks	Chankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.054	-0.04 (-0.10 to 0.02)	0.169
Pyrexia	120U 12 (one time injection) weeks	Chrankrachang, 2011[7] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.054	-0.04 (-0.10 to 0.02)	0.169
Pyrexia	All doses	Pooled	22/418	12/169	0.5 (0.1 to 1.3)	1	-0.04 (-0.09 to 0.01)	1

Appendix Table D125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Edema	Chankrachang, 2011[f] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Eyelid edema	Elkind, 2006[6] Low	25 vs. 7.5	0/101	1/105	0.3 (0.0 to 8.4)	-0.01 (-0.04 to 0.02)
Eyelid edema	Elkind, 2006[6] **Low**	**50 vs. 25**	**7/106**	**0/101**	**14.3 (0.8 to 247.2)**	**0.07 (0.02 to 0.12)**
Eyelid edema	Elkind, 2006[6] **Low**	**50 vs. 7.5**	**7/106**	**1/105**	**6.9 (0.9 to 55.4)**	**0.06 (0.01 to 0.11)**
Eyelid edema	Relja, 2007[16] Low	150 vs. 75	0/125	2/123	0.2 (0.0 to 4.1)	-0.02 (-0.04 to 0.01)
Eyelid edema	Relja, 2007[16] Low	225 vs. 150	3/129	0/125	6.8 (0.4 to 130.0)	0.02 (-0.01 to 0.05)
Eyelid edema	Relja, 2007[16] Low	225 vs. 75	3/129	2/123	1.4 (0.2 to 8.4)	0.01 (-0.03 to 0.04)
Eyelid edema	Chankrachang, 2011[f] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Rash	Relja, 2007[16] Low	150 vs. 75	0/125	3/123	0.1 (0.0 to 2.7)	-0.02 (-0.06 to 0.01)
Rash	Relja, 2007[16] Low	225 vs. 150	1/129	0/125	2.9 (0.1 to 70.7)	0.01 (-0.01 to 0.03)
Rash	Relja, 2007[16] Low	225 vs. 75	1/129	3/123	0.3 (0.0 to 3.0)	-0.02 (-0.05 to 0.01)
Adverse effects	Saper, 2007[3] Low	9 vs. 6	11/49	8/45	1.3 (0.6 to 2.9)	0.05 (-0.11 to 0.21)
Adverse effects	Saper, 2007[3] Low	10 vs. 6	9/44	8/45	1.2 (0.5 to 2.7)	0.03 (-0.14 to 0.19)
Adverse effects	Saper, 2007[3] Low	10 vs. 9	9/44	11/49	0.9 (0.4 to 2.0)	-0.02 (-0.19 to 0.15)
Adverse effects	Saper, 2007[3] Low	25 vs. 10	17/49	9/44	1.7 (0.8 to 3.4)	0.14 (-0.04 to 0.32)
Adverse effects	Saper, 2007[3] **Low**	**25 vs. 6**	**17/49**	**8/45**	**2.0 (0.9 to 4.1)**	**0.17 (0.00 to 0.34)**
Adverse effects	Saper, 2007[3] Low	25 vs. 9	17/49	11/49	1.5 (0.8 to 3.0)	0.12 (-0.05 to 0.30)
Adverse effects	Elkind, 2006[6] Low	25 vs. 7.5	47/101	52/105	0.9 (0.7 to 1.2)	-0.03 (-0.17 to 0.11)
Adverse effects	Elkind, 2006[6] Low	50 vs. 25	60/106	47/101	1.2 (0.9 to 1.6)	0.10 (-0.03 to 0.24)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Adverse effects	Elkind, 2006[6] Low	50 vs. 7.5	60/106	52/105	1.1 (0.9 to 1.5)	0.07 (-0.06 to 0.21)
Adverse effects	Relja, 2007[16] Low	150 vs. 75	79/125	77/123	1.0 (0.8 to 1.2)	0.01 (-0.11 to 0.13)
Adverse effects	Silberstein, 2005[10] Low	150 vs. 75	92/168	97/174	1.0 (0.8 to 1.2)	-0.01 (-0.12 to 0.10)
Adverse effects	**Petri, 2009[8] High**	**210 vs. 80**	**12/32**	**4/32**	**3.0 (1.1 to 8.3)**	**0.25 (0.05 to 0.45)**
Adverse effects	Relja, 2007[16] Low	225 vs. 150	87/129	79/125	1.1 (0.9 to 1.3)	0.04 (-0.07 to 0.16)
Adverse effects	Relja, 2007[16] Low	225 vs. 75	87/129	77/123	1.1 (0.9 to 1.3)	0.05 (-0.07 to 0.17)
Adverse effects	Silberstein, 2005[10] **Low**	**225 vs. 150**	**119/182**	**92/168**	**1.2 (1.0 to 1.4)**	**0.11 (0.00 to 0.21)**
Adverse effects	Silberstein, 2005[10] **Low**	**225 vs. 75**	**119/182**	**97/174**	**1.2 (1.0 to 1.4)**	**0.10 (0.00 to 0.20)**
Adverse effects	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	139/180	135/173	1.0 (0.9 to 1.1)	-0.01 (-0.10 to 0.08)
Mastication disorder	Chankrachang, 2011[f] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Menorrhagia	Chankrachang, 2011[f] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Bronchitis	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	10/180	6/173	1.6 (0.6 to 4.3)	0.02 (-0.02 to 0.06)
Flu syndrome	Elkind, 2006[6] Low	25 vs. 7.5	4/101	11/105	0.4 (0.1 to 1.1)	-0.07 (-0.13 to 0.00)
Flu syndrome	Elkind, 2006[6] Low	50 vs. 25	7/106	4/101	1.7 (0.5 to 5.5)	0.03 (-0.03 to 0.09)
Flu syndrome	Elkind, 2006[6] Low	50 vs. 7.5	7/106	11/105	0.6 (0.3 to 1.6)	-0.04 (-0.11 to 0.04)
Flu syndrome	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	14/180	12/173	1.1 (0.5 to 2.4)	0.01 (-0.05 to 0.06)
Herpes zoster	Chankrachang, 2011[f] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Infection	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	15/180	20/173	0.7 (0.4 to 1.4)	-0.03 (-0.09 to 0.03)
Respiratory infection	Elkind, 2006[6] Low	25 vs. 7.5	10/101	12/105	0.9 (0.4 to 1.9)	-0.02 (-0.10 to 0.07)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Respiratory infection	Elkind, 2006[6] Low	50 vs. 25	11/106	10/101	1.0 (0.5 to 2.4)	0.00 (-0.08 to 0.09)
Respiratory infection	Elkind, 2006[6] Low	50 vs. 7.5	11/106	12/105	0.9 (0.4 to 2.0)	-0.01 (-0.09 to 0.07)
Respiratory infection	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	12/180	14/173	0.8 (0.4 to 1.7)	-0.01 (-0.07 to 0.04)
Sinus infection	Elkind, 2006[6] Low	25 vs. 7.5	7/101	4/105	1.8 (0.5 to 6.0)	0.03 (-0.03 to 0.09)
Sinus infection	Elkind, 2006[6] Low	50 vs. 25	4/106	7/101	0.5 (0.2 to 1.8)	-0.03 (-0.09 to 0.03)
Sinus infection	Elkind, 2006[6] Low	50 vs. 7.5	4/106	4/105	1.0 (0.3 to 3.9)	0.00 (-0.05 to 0.05)
Sinus infection	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	15/180	16/173	0.9 (0.5 to 1.8)	-0.01 (-0.07 to 0.05)
Injection site haemorrhage	Relja, 2007[16] Low	150 vs. 75	2/125	3/123	0.7 (0.1 to 3.9)	-0.01 (-0.04 to 0.03)
Injection site haemorrhage	Relja, 2007[16] Low	225 vs. 150	0/129	2/125	0.2 (0.0 to 4.0)	-0.02 (-0.04 to 0.01)
Injection site haemorrhage	Relja, 2007[16] Low	225 vs. 75	0/129	3/123	0.1 (0.0 to 2.6)	-0.02 (-0.06 to 0.01)
Injection site pain	Relja, 2007[16] Low	150 vs. 75	9/125	4/123	2.2 (0.7 to 7.0)	0.04 (-0.02 to 0.09)
Injection site pain	Relja, 2007[16] Low	225 vs. 150	3/129	9/125	0.3 (0.1 to 1.2)	-0.05 (-0.10 to 0.00)
Injection site pain	Relja, 2007[16] Low	225 vs. 75	3/129	4/123	0.7 (0.2 to 3.1)	-0.01 (-0.05 to 0.03)
Injection site pain	Chankrachang, 2011[f] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Injection site weakness	Silberstein, 2000[5] Moderate	75 vs. 25	5/40	4/42	1.3 (0.4 to 4.5)	0.03 (-0.11 to 0.17)
Injection-site pain	Silberstein, 2005[10] Low	150 vs. 75	10/168	8/174	1.3 (0.5 to 3.2)	0.01 (-0.03 to 0.06)
Injection-site pain	Silberstein, 2005[10] Low	225 vs. 150	17/182	10/168	1.6 (0.7 to 3.3)	0.03 (-0.02 to 0.09)
Injection-site pain	Silberstein, 2005[10] Low	225 vs. 75	17/182	8/174	2.0 (0.9 to 4.6)	0.05 (-0.01 to 0.10)
Injection-site stinging	Silberstein, 2005[10] Low	150 vs. 75	5/168	2/174	2.6 (0.5 to 13.2)	0.02 (-0.01 to 0.05)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Injection-site stinging	Silberstein, 2005[10] Low	225 vs. 150	3/182	5/168	0.6 (0.1 to 2.3)	-0.01 (-0.04 to 0.02)
Injection-site stinging	Silberstein, 2005[10] Low	225 vs. 75	3/182	2/174	1.4 (0.2 to 8.5)	0.00 (-0.02 to 0.03)
Pyrexia	Chankrachang, 2011[7] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Blepharoptosis	Saper, 2007[3] Low	9 vs. 6	0/49	1/45	0.3 (0.0 to 7.3)	-0.02 (-0.08 to 0.04)
Blepharoptosis	Saper, 2007[3] Low	10 vs. 6	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Blepharoptosis	Saper, 2007[3] Low	10 vs. 9	0/44	0/49	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Blepharoptosis	Saper, 2007[3] Low	25 vs. 10	4/49	0/44	8.1 (0.4 to 146.3)	0.08 (0.00 to 0.17)
Blepharoptosis	Saper, 2007[3] Low	25 vs. 6	4/49	1/45	3.7 (0.4 to 31.7)	0.06 (-0.03 to 0.15)
Blepharoptosis	Saper, 2007[3] Low	25 vs. 9	4/49	0/49	9.0 (0.5 to 162.8)	0.08 (0.00 to 0.17)
Blepharoptosis	Elkind, 2006[6] Low	25 vs. 7.5	5/101	2/105	2.6 (0.5 to 13.1)	0.03 (-0.02 to 0.08)
Blepharoptosis	Elkind, 2006[6] Low	50 vs. 25	8/106	5/101	1.5 (0.5 to 4.5)	0.03 (-0.04 to 0.09)
Blepharoptosis	Elkind, 2006[6]18329 Low	50 vs. 7.5	8/106	2/105	4.0 (0.9 to 18.2)	0.06 (0.00 to 0.11)
Blepharoptosis	Silberstein, 2000[5] Moderate	75 vs. 25	7/40	6/42	1.2 (0.5 to 3.3)	0.03 (-0.13 to 0.19)
Blepharoptosis	**Relja, 2007[16] Low**	**150 vs. 75**	**12/125**	**3/123**	**3.9 (1.1 to 13.6)**	**0.07 (0.01 to 0.13)**
Blepharoptosis	Silberstein, 2005[10] Low	150 vs. 75	7/168	6/174	1.2 (0.4 to 3.5)	0.01 (-0.03 to 0.05)
Blepharoptosis	Relja, 2007[16] Low	225 vs. 150	18/129	12/125	1.5 (0.7 to 2.9)	0.04 (-0.04 to 0.12)
Blepharoptosis	**Relja, 2007[16] Low**	**225 vs. 75**	**18/129**	**3/123**	**5.7 (1.7 to 18.9)**	**0.12 (0.05 to 0.18)**
Blepharoptosis	Silberstein, 2005[10] Low	225 vs. 150	12/182	7/168	1.6 (0.6 to 3.9)	0.02 (-0.02 to 0.07)
Blepharoptosis	Silberstein, 2005[10] Low	225 vs. 75	12/182	6/174	1.9 (0.7 to 5.0)	0.03 (-0.01 to 0.08)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Blepharoptosis	Chankrachang, 2011[7] Risk of bias Low	240 vs. 120	2/43	0/43	5.0 (0.2 to 101.2)	0.05 (-0.03 to 0.12)
Blepharoptosis	Elkind, 2006[6] Low	7.5or 50 vs. 7.5 or 25	16/180	7/173	2.2 (0.9 to 5.2)	0.05 (0.00 to 0.10)
Muscle tightness	Chankrachang, 2011[7] Low	240 vs. 120	0/43	2/43	0.2 (0.0 to 4.0)	-0.05 (-0.12 to 0.03)
Muscle weakness	Saper, 2007[3] Low	9 vs. 6	0/49	0/45	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[3] Low	10 vs. 6	0/44	0/45	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[3] Low	10 vs. 9	0/44	0/49	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[3] **Low**	**25 vs. 10**	**6/49**	**0/44**	**11.7 (0.7 to 201.9)**	**0.12 (0.02 to 0.22)**
Muscle weakness	**Saper, 2007[3]** **Low**	**25 vs. 6**	**6/49**	**0/45**	**12.0 (0.7 to 206.4)**	**0.12 (0.02 to 0.22)**
Muscle weakness	**Saper, 2007[3]** **Low**	**25 vs. 9**	**6/49**	**0/49**	**13.0 (0.8 to 224.7)**	**0.12 (0.03 to 0.22)**
Muscle weakness	Relja, 2007[16] Low	150 vs. 75	35/125	30/123	1.1 (0.8 to 1.7)	0.04 (-0.07 to 0.15)
Muscle weakness	**Silberstein, 2005[10]** **Low**	**150 vs. 75**	**44/168**	**29/174**	**1.6 (1.0 to 2.4)**	**0.10 (0.01 to 0.18)**
Muscle weakness	Relja, 2007[16] Low	225 vs. 150	35/129	35/125	1.0 (0.7 to 1.4)	-0.01 (-0.12 to 0.10)
Muscle weakness	Relja, 2007[16] Low	225 vs. 75	35/129	30/123	1.1 (0.7 to 1.7)	0.03 (-0.08 to 0.14)
Muscle weakness	Silberstein, 2005[10] Low	225 vs. 150	56/182	44/168	1.2 (0.8 to 1.6)	0.05 (-0.05 to 0.14)
Muscle weakness	**Silberstein, 2005[10]** **Low**	**225 vs. 75**	**56/182**	**29/174**	**1.8 (1.2 to 2.7)**	**0.14 (0.05 to 0.23)**
Musculoskeletal stiffness	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Neck rigidity	Relja, 2007[16] Low	150 vs. 75	20/125	13/123	1.5 (0.8 to 2.9)	0.05 (-0.03 to 0.14)
Neck rigidity	Silberstein, 2005[10] Low	150 vs. 75	14/168	14/174	1.0 (0.5 to 2.1)	0.00 (-0.06 to 0.06)
Neck rigidity	Relja, 2007[16] Low	225 vs. 150	22/129	20/125	1.1 (0.6 to 1.9)	0.01 (-0.08 to 0.10)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Neck rigidity	Relja, 2007[16] Low	225 vs. 75	22/129	13/123	1.6 (0.9 to 3.1)	0.06 (-0.02 to 0.15)
Neck rigidity	**Silberstein, 2005[10] Low**	**225 vs. 150**	**27/182**	**14/168**	**1.8 (1.0 to 3.3)**	**0.07 (0.00 to 0.13)**
Neck rigidity	**Silberstein, 2005[10] Low**	**225 vs. 75**	**27/182**	**14/174**	**1.8 (1.0 to 3.4)**	**0.07 (0.00 to 0.13)**
Skin tightness	Relja, 2007[16] Low	150 vs. 75	9/125	7/123	1.3 (0.5 to 3.3)	0.02 (-0.05 to 0.08)
Skin tightness	Relja, 2007[16] Low	225 vs. 150	6/129	9/125	0.6 (0.2 to 1.8)	-0.03 (-0.08 to 0.03)
Skin tightness	Relja, 2007[16] Low	225 vs. 75	6/129	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.07 to 0.04)
Tenderness	Chankrachang, 2011[f] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Diplopia	Silberstein, 2000[5] Moderate	75 vs. 25	2/40	0/42	5.2 (0.3 to 106.0)	0.05 (-0.03 to 0.13)
Dizziness	Relja, 2007[16] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Dizziness	Relja, 2007[16] Low	225 vs. 150	2/129	3/125	0.6 (0.1 to 3.8)	-0.01 (-0.04 to 0.03)
Dizziness	Relja, 2007[16] Low	225 vs. 75	2/129	3/123	0.6 (0.1 to 3.7)	-0.01 (-0.04 to 0.03)
Dizziness	Chankrachang, 2011[f] Low	240 vs. 120	1/43	2/43	0.5 (0.0 to 5.3)	-0.02 (-0.10 to 0.05)
Dizziness	Elkind, 2006[6] Low	7.5 or 50 vs. 7.5 or 25	9/180	2/173	4.3 (0.9 to 19.7)	0.04 (0.00 to 0.07)
Dyskinesia	Chankrachang, 2011[f] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Dysphagia	Relja, 2007[16] Low	150 vs. 75	3/125	1/123	3.0 (0.3 to 28.0)	0.02 (-0.02 to 0.05)
Dysphagia	Silberstein, 2005[10] Low	150 vs. 75	5/168	3/174	1.7 (0.4 to 7.1)	0.01 (-0.02 to 0.04)
Dysphagia	Relja, 2007[16] Low	225 vs. 150	4/129	3/125	1.3 (0.3 to 5.7)	0.01 (-0.03 to 0.05)
Dysphagia	Relja, 2007[16] Low	225 vs. 75	4/129	1/123	3.8 (0.4 to 33.6)	0.02 (-0.01 to 0.06)
Dysphagia	Silberstein, 2005[10] Low	225 vs. 150	11/182	5/168	2.0 (0.7 to 5.7)	0.03 (-0.01 to 0.07)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Dysphagia	Silberstein, 2005[10] Low	225 vs. 75	11/182	3/174	3.5 (1.0 to 12.4)	0.04 (0.00 to 0.08)
Hypertonia	Relja, 2007[16] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Hypertonia	Silberstein, 2005[10] Low	150 vs. 75	15/168	13/174	1.2 (0.6 to 2.4)	0.01 (-0.04 to 0.07)
Hypertonia	Relja, 2007[16] Low	225 vs. 150	4/129	3/125	1.3 (0.3 to 5.7)	0.01 (-0.03 to 0.05)
Hypertonia	Relja, 2007[16] Low	225 vs. 75	4/129	3/123	1.3 (0.3 to 5.6)	0.01 (-0.03 to 0.05)
Hypertonia	Silberstein, 2005[10] Low	225 vs. 150	13/182	15/168	0.8 (0.4 to 1.6)	-0.02 (-0.07 to 0.04)
Hypertonia	Silberstein, 2005[10] Low	225 vs. 75	13/182	13/174	1.0 (0.5 to 2.0)	0.00 (-0.06 to 0.05)
Hypesthesia	Silberstein, 2005[10] Low	150 vs. 75	11/168	11/174	1.0 (0.5 to 2.3)	0.00 (-0.05 to 0.05)
Hypesthesia	Silberstein, 2005[10] Low	225 vs. 150	12/182	11/168	1.0 (0.5 to 2.2)	0.00 (-0.05 to 0.05)
Hypesthesia	Silberstein, 2005[10] Low	225 vs. 75	12/182	11/174	1.0 (0.5 to 2.3)	0.00 (-0.05 to 0.05)
Hypoesthesia	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Nausea	Relja, 2007[16] Low	150 vs. 75	2/125	1/123	2.0 (0.2 to 21.4)	0.01 (-0.02 to 0.03)
Nausea	Relja, 2007[16] Low	225 vs. 150	4/129	2/125	1.9 (0.4 to 10.4)	0.02 (-0.02 to 0.05)
Nausea	Relja, 2007[16] Low	225 vs. 75	4/129	1/123	3.8 (0.4 to 33.6)	0.02 (-0.01 to 0.06)
Nausea	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Paraesthesia	Relja, 2007[16] Low	150 vs. 75	4/125	4/123	1.0 (0.3 to 3.8)	0.00 (-0.04 to 0.04)
Paraesthesia	Relja, 2007[16] Low	225 vs. 150	6/129	4/125	1.5 (0.4 to 5.0)	0.01 (-0.03 to 0.06)
Paraesthesia	Relja, 2007[16] Low	225 vs. 75	6/129	4/123	1.4 (0.4 to 4.9)	0.01 (-0.03 to 0.06)
Sedation	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Somnolence	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Trismus	Chankrachang, 2011[7] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Vomiting	Chankrachang, 2011[7] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Arm pain	Relja, 2007[16] Low	150 vs. 75	6/125	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.06 to 0.05)
Arm pain	Relja, 2007[16] Low	225 vs. 150	6/129	6/125	1.0 (0.3 to 2.9)	0.00 (-0.05 to 0.05)
Arm pain	Relja, 2007[16] Low	225 vs. 75	6/129	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.07 to 0.04)
Asthenia	Relja, 2007[16] Low	150 vs. 75	3/125	4/123	0.7 (0.2 to 3.2)	-0.01 (-0.05 to 0.03)
Asthenia	Silberstein, 2005[10] Low	150 vs. 75	6/168	1/174	6.2 (0.8 to 51.1)	0.03 (0.00 to 0.06)
Asthenia	Relja, 2007[16] Low	225 vs. 150	5/129	3/125	1.6 (0.4 to 6.6)	0.01 (-0.03 to 0.06)
Asthenia	Relja, 2007[16] Low	225 vs. 75	5/129	4/123	1.2 (0.3 to 4.3)	0.01 (-0.04 to 0.05)
Asthenia	Silberstein, 2005[10] Low	225 vs. 150	2/182	6/168	0.3 (0.1 to 1.5)	-0.02 (-0.06 to 0.01)
Asthenia	Silberstein, 2005[10] Low	225 vs. 75	2/182	1/174	1.9 (0.2 to 20.9)	0.01 (-0.01 to 0.02)
Back pain	Silberstein, 2005[10] Low	150 vs. 75	4/168	3/174	1.4 (0.3 to 6.1)	0.01 (-0.02 to 0.04)
Back pain	Silberstein, 2005[10] Low	225 vs. 150	6/182	4/168	1.4 (0.4 to 4.8)	0.01 (-0.03 to 0.04)
Back pain	Silberstein, 2005[10] Low	225 vs. 75	6/182	3/174	1.9 (0.5 to 7.5)	0.02 (-0.02 to 0.05)
Face pain	Relja, 2007[16] Low	150 vs. 75	6/125	4/123	1.5 (0.4 to 5.1)	0.02 (-0.03 to 0.06)
Face pain	Relja, 2007[16] Low	225 vs. 150	4/129	6/125	0.6 (0.2 to 2.2)	-0.02 (-0.06 to 0.03)
Face pain	Relja, 2007[16] Low	225 vs. 75	4/129	4/123	1.0 (0.2 to 3.7)	0.00 (-0.04 to 0.04)
Headache	Saper, 2007[3] Low	9 vs. 6	0/49	2/45	0.2 (0.0 to 3.7)	-0.04 (-0.12 to 0.03)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Headache	Saper, 2007[3] Low	10 vs. 6	1/44	2/45	0.5 (0.0 to 5.4)	-0.02 (-0.10 to 0.05)
Headache	Saper, 2007[3] Low	10 vs. 9	1/44	0/49	3.3 (0.1 to 79.8)	0.02 (-0.04 to 0.08)
Headache	Saper, 2007[3] Low	25 vs. 10	3/49	1/44	2.7 (0.3 to 25.0)	0.04 (-0.04 to 0.12)
Headache	Saper, 2007[3] Low	25 vs. 6	3/49	2/45	1.4 (0.2 to 7.9)	0.02 (-0.07 to 0.11)
Headache	Saper, 2007[3] Low	25 vs. 9	3/49	0/49	7.0 (0.4 to 132.0)	0.06 (-0.01 to 0.14)
Headache	Elkind, 2006[6] Low	25 vs. 7.5	2/101	1/105	2.1 (0.2 to 22.6)	0.01 (-0.02 to 0.04)
Headache	Elkind, 2006[6] Low	50 vs. 25	8/106	2/101	3.8 (0.8 to 17.5)	0.06 (0.00 to 0.11)
Headache	**Elkind, 2006[6] Low**	**50 vs. 7.5**	**8/106**	**1/105**	**7.9 (1.0 to 62.3)**	**0.07 (0.01 to 0.12)**
Headache	Relja, 2007[16] Low	150 vs. 75	5/125	4/123	1.2 (0.3 to 4.5)	0.01 (-0.04 to 0.05)
Headache	Silberstein, 2005[10] Low	150 vs. 75	14/168	7/174	2.1 (0.9 to 5.0)	0.04 (-0.01 to 0.09)
Headache	Relja, 2007[16] Low	225 vs. 150	2/129	5/125	0.4 (0.1 to 2.0)	-0.02 (-0.06 to 0.02)
Headache	Relja, 2007[16] Low	225 vs. 75	2/129	4/123	0.5 (0.1 to 2.6)	-0.02 (-0.05 to 0.02)
Headache	Silberstein, 2005[10] Low	225 vs. 150	15/182	14/168	1.0 (0.5 to 2.0)	0.00 (-0.06 to 0.06)
Headache	Silberstein, 2005[10] Low	225 vs. 75	15/182	7/174	2.0 (0.9 to 4.9)	0.04 (-0.01 to 0.09)
Headache	Chankrachang, 2011[f] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Headache	Elkind, 2006[6] Low	7.5 or 50 vs. 7.5 or 25	10/180	8/173	1.2 (0.5 to 3.0)	0.01 (-0.04 to 0.06)
Infection site pain	Elkind, 2006[6] Low	7.5 or 50 vs. 7.5 or 25	4/180	9/173	0.4 (0.1 to 1.4)	-0.03 (-0.07 to 0.01)
Malaise	Relja, 2007[16] Low	150 vs. 75	0/125	0/123	0.0 (0.0 to 0.0)	0.00 (-0.02 to 0.02)
Malaise	Relja, 2007[16] Low	225 vs. 150	4/129	0/125	8.7 (0.5 to 160.4)	0.03 (0.00 to 0.06)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Malaise	Relja, 2007[16] Low	225 vs. 75	4/129	0/123	8.6 (0.5 to 157.8)	0.03 (0.00 to 0.06)
Migraine	Relja, 2007[16] Low	150 vs. 75	3/125	2/123	1.5 (0.3 to 8.7)	0.01 (-0.03 to 0.04)
Migraine	Silberstein, 2005[10] Low	150 vs. 75	5/168	2/174	2.6 (0.5 to 13.2)	0.02 (-0.01 to 0.05)
Migraine	Relja, 2007[16] Low	225 vs. 150	1/129	3/125	0.3 (0.0 to 3.1)	-0.02 (-0.05 to 0.01)
Migraine	Relja, 2007[16] Low	225 vs. 75	1/129	2/123	0.5 (0.0 to 5.2)	-0.01 (-0.04 to 0.02)
Migraine	Silberstein, 2005[10] Low	225 vs. 150	0/182	5/168	0.1 (0.0 to 1.5)	-0.03 (-0.06 to 0.00)
Migraine	Silberstein, 2005[10] Low	225 vs. 75	0/182	2/174	0.2 (0.0 to 4.0)	-0.01 (-0.03 to 0.01)
Myalgia	Relja, 2007[16] Low	150 vs. 75	5/125	7/123	0.7 (0.2 to 2.2)	-0.02 (-0.07 to 0.04)
Myalgia	Relja, 2007[16] Low	225 vs. 150	10/129	5/125	1.9 (0.7 to 5.5)	0.04 (-0.02 to 0.10)
Myalgia	Relja, 2007[16] Low	225 vs. 75	10/129	7/123	1.4 (0.5 to 3.5)	0.02 (-0.04 to 0.08)
Neck pain	Relja, 2007[16] Low	150 vs. 75	24/125	22/123	1.1 (0.6 to 1.8)	0.01 (-0.08 to 0.11)
Neck pain	Silberstein, 2005[10] Low	150 vs. 75	37/168	30/174	1.3 (0.8 to 2.0)	0.05 (-0.04 to 0.13)
Neck pain	Relja, 2007[16] Low	225 vs. 150	30/129	24/125	1.2 (0.8 to 2.0)	0.04 (-0.06 to 0.14)
Neck pain	Relja, 2007[16] Low	225 vs. 75	30/129	22/123	1.3 (0.8 to 2.1)	0.05 (-0.05 to 0.15)
Neck pain	Silberstein, 2005[10] Low	225 vs. 150	41/182	37/168	1.0 (0.7 to 1.5)	0.01 (-0.08 to 0.09)
Neck pain	Silberstein, 2005[10] Low	225 vs. 75	41/182	30/174	1.3 (0.9 to 2.0)	0.05 (-0.03 to 0.14)
Neck pain	Chankrachang, 2011[f] Low	240 vs. 120	0/43	2/43	0.2 (0.0 to 4.0)	-0.05 (-0.12 to 0.03)
Pain	Relja, 2007[16] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Pain	Relja, 2007[16] Low	225 vs. 150	5/129	3/125	1.6 (0.4 to 6.6)	0.01 (-0.03 to 0.06)

Appendix Table 125. Dose response adverse effects with botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effect	Reference Risk of bias	Dose of botox, units	Events/ randomized Larger dose	Events/ randomized Smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Pain	Relja, 2007[16] Low	225 vs. 75	5/129	3/123	1.6 (0.4 to 6.5)	0.01 (-0.03 to 0.06)
Pain	Elkind, 2006[6] Low	7.5 or 50 vs. 7.5 or 25	14/180	13/173	1.0 (0.5 to 2.1)	0.00 (-0.05 to 0.06)
Radicular pain	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Shoulder / arm pain	Silberstein, 2005[10] Low	150 vs. 75	11/168	8/174	1.4 (0.6 to 3.5)	0.02 (-0.03 to 0.07)
Shoulder / arm pain	Silberstein, 2005[10] Low	225 vs. 150	12/182	11/168	1.0 (0.5 to 2.2)	0.00 (-0.05 to 0.05)
Shoulder / arm pain	Silberstein, 2005[10] Low	225 vs. 75	12/182	8/174	1.4 (0.6 to 3.4)	0.02 (-0.03 to 0.07)
Tension headache	Chankrachang, 2011[7] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)

CI – confidence interval

Appendix Table D126. Randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Country where study was conducted	Total sample [number analyzed] % females	Age	Definition of migraine	Presence of aura	Duration of migraine	Migraine frequency/ month	Baseline comorbidity
Storey, 2001[17]	Not reported	40 [Not reported] 97.5% female	Mean 38.2 years	International Headache Society (IHS) criteria	Not reported	Not reported	4.7	Not reported
Edwards, 2003[18]	Previously reported	70 [70] 97.1% female	Mean 41.1 years	International Headache Society criteria	Not reported	Not reported	4.5	Not reported
Silvestrini, 2003[19]	Italy	28 [28] 64.3% female	Mean 43.5 years	International Headache Society criteria	All patients had a history of migraine without aura attacks as inclusion criterion	3 years	20	Not reported
Brandes, 2004[21]	North America	483 [468] 86.8% female	Mean 38.9 years	International Headache Society (IHS) criteria	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2004[22]	USA	487 [469] 89.1% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2004[23]	Italy	115 [72] 54.2% female	Mean 39.2 years	International Headache Society (1988) criteria	Patients with migraine without aura,n(%): Topiramate: 27 (77), Placebo: 31 (84)	Not reported	5.5	Not reported
Bussone, 2005[24]	Not reported (Pooled analysis)	758 [756] 84.3% female	Mean 39.8 years	International Headache Society criteria	Not reported	Not reported	5.4	Not reported
Silberstein, 2006[26]	USA	469 (ITT population). Number randomized not given [469] 88.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported

Appendix Table 126. Randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Country where study was conducted	Total sample [number analyzed] % females	Age	Definition of migraine	Presence of aura	Duration of migraine	Migraine frequency/ month	Baseline comorbidity
Mei, 2006[27]	Italy	50 [35] 68.6% female	Mean 45.9 years	International Classification of Headache Disorders 2nd Edition	Not reported	4.97 years	Not reported	Not reported
Silberstein, 2006[28]	USA	213 [Variable] 85.8% female	Mean 40.5 years	International Headache Society criteria	75 subjects had migraine with aura	Not reported	4.9	Not reported
Brandes, 2006[29]	USA	483 [468] 86.8% female	Mean 38.9 years	International Headache Society criteria for migraine with or without aura	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2007[30]	USA	328 [Variable] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration:9.2 years; Age at onset (years): 19.7	Not reported	Not reported
Diener, 2007[33]	Not reported	59 [59] 74.5% female	Mean 46 years	Second edition of The International Classification of Headache Disorders criteria	Not reported	At least 1 year	Not reported	Beck Depression Inventory, mean (SD): Placebo: 13.4(8.8), Topiramate: 9.0 (7.0)
Lainez, 2007[34]	Not reported	774 [758] 84.4% female	Mean 39.9 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported
Diener, 2007[37]	21 countries in Europe	818 in open-label phase and 514 in the double-blind phase [Not reported] 89.0% female	Mean 40·1 years	International Headache Society criteria	Not reported	Not reported	8.7	Not reported
Adelman, 2008[39]	USA, Australia, Canada, Denmark, Finland,	1580 [1580] 85.0% female	Mean 40.1 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported

Appendix Table 126. Randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Country where study was conducted	Total sample [number analyzed] % females	Age	Definition of migraine	Presence of aura	Duration of migraine	Migraine frequency/ month	Baseline comorbidity
	France, Germany, Italy, Korea, the Netherlands, South Africa, Spain, Sweden, Taiwan, and the United Kingdom							
Silberstein, 2009[40]	USA	328 [321] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration:9.2 years; Age at onset (years): 19.7	Not reported	Not reported
Lipton, 2011[41]	Not reported	385 [Variable] 10.9% female	Mean 40.3 years	International Headache Society criteria 1.1,1.2	Not reported	Age at migraine onset (years): 20.3	Not reported	Not reported

Appendix Table D127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
Storey, 2001[17]	Industry	Yes	Yes	Not reported	Not applicable
Edwards, 2003[18]	Industry	Yes	Yes	Yes	Ms. Potter is on the Speakers' Bureau for biogen, GlaxoSmithKline and Ortho-McNeil Pharmaceutical, Inc, and has received funding from Biogen, Ortho-McNeil Pharmaceutical, Inc, Pfizer Inc, Wyeth Pharmaceuticals for previous research
Silvestrini, 2003[19]	Not reported	Yes	Yes	Not reported	Not applicable
Brandes, 2004[21]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, Allergan, UCB Pharma, Johnson & Johnson, AstraZeneca, Pfizer, Bristol Myers-Squibb, Winston Laboratories, Forest Laboratories, Sanofi-Synthelabo, and Elan Pharmaceuticals; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Merck, Allergan, Pfizer, Pharmacia, Ortho-McNeil, and UCB Pharma; has served as a consultant to Merck, GlaxoSmithKline, Pfizer, AstraZeneca, Allergan, and Ortho-McNeil; and has received educational funding from GlaxoSmithKline. Dr Saper has received research grants from GlaxoSmithKline, AstraZeneca, Merck, Abbott, Allergan, Elan, Pfizer, Ortho-McNeil, and Novartis; has served on advisory boards or as a consultant for AstraZeneca, GlaxoSmithKline, Allergan, Ortho-McNeil, and Medtronic; and has served on the speakers bureau for GlaxoSmithKline, Merck, AstraZeneca, Ortho-McNeil, Pfizer, and Xcel. Dr Diamond has served as a speaker, consultant, or both or has conducted research for AstraZeneca, Bristol-Myers Squibb, Ortho- McNeil, Elan, GlaxoSmithKline, Merck, and Pfizer. Dr Couch has participated in research for, been an advisory board member of, and served as a speaker for Ortho-McNeil.
Silbersein, 2004[22]	Industry	Yes	Yes	Yes	Silberstein is on the advisory panel of, speakers bureau of, or serves as a consultant for Abbott Laboratories, Allergan, Inc, AstraZeneca, Elan Pharmaceutical Research Corp, Eli Lilly, Ortho-McNeil Pharmaceutical, Merck & Co, and GlaxoSmithKline; receives research support from Allergan, Inc, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Merck & Co, Ortho-McNeil Pharmaceutical, Pfizer, Inc, UCB Pharma, and Vernalis; and has received educational grants from Abbott Laboratories, Allergan, Inc, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck & Co, Ortho-McNeil Pharmaceutical, and Parke-Davis. Drs Neto and Jacobs and Ms Schmitt hold shares in Johnson & Johnson Pharmaceutical Research and Development, LLC, a subsidiary of Johnson & Johnson Corporation.
Mei, 2004[23]	Not reported	Yes	Yes	Not reported	Not applicable

Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
Bussone, 2005[24]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[26]	Industry	Yes	Yes	Yes	George Papadopoulos is from Johnson and Johnson Pharmaceutical Services, LLC, Raritan, NJ, USA and Steven Greenberg from Ortho-McNeil Neurologies, Titusville, NJ, USA. Personnel of Pharmaceutical Research and Development , Ortho-McNeil Neurologics, Inc, Titusville, New Jersey, and Phase Five Communications, New York, New York, contributed to the preparation of the manuscript
Mei, 2006[27]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[28]	Industry	Yes	Yes	Not reported	Not applicable
Brandes, 2006[29]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck & Co, Inc, GlaxoSmithKline, UCB Pharma, Allergan Inc, Johnson & Johnson, Astra-Zeneca Pharmaceuticals LP, Pfizer Inc, Bristol-Meyers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Inc, Novartis, Endo Pharmaceuticals, Pozen, Vernalis, Ortho-McNeil, and Advanced Bionics; has served on the speaker's bureau for GlaxoSmith-Kline, AstraZeneca Pharmaceuticals LP, Pfizer Inc, Merck & Co, Inc, Ortho-McNeil, Allergan Inc, MedPointe Pharmaceuticals, Endo Pharmaceuticals, UCB Pharma; has served as a consultant to Merck & Co, Inc, GlaxoSmithKline, Pfizer Inc, AstraZeneca Pharmaceuticals LP, Allergan Inc, Ortho-McNeil, and Aradigm Corp; and has received an educational grant from GlaxoSmithKline. Dr Kudrow has been on a speaker's bureau of GlaxoSmithKline and Ortho-McNeil and has received grant and research support from Ortho-McNeil, GlaxoSmithKline, Pozen, Merck & Co, Inc, and Eisai Inc. Dr Fairclough received financial support as a consultant to perform analyses of the data in this study. Drs Rupnow and Greenberg are fulltime employees of Johnson & Johnson. Dr Rothrock has served as a paid consultant to Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pozen, and Allergan Inc; has received research support from those companies and from Abbott Laboratories, Elan Corporation, Esai Inc, and AstraZeneca Pharmaceuticals LP; and has received honoraria for lecturing from Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Elan Corporation, and Endo Pharmaceuticals.
Silberstein, 2007[30]	Industry	Yes	Yes	Yes	Dr. Silberstein has received personal compensation for activities with: GlaxoSmith-Kline, Inc., Johnson & Johnson, Merck & Co., Inc., UCB Pharma, AstraZeneca Pharmaceuticals, Inc., Pfizer, Inc., Allergan, Inc., Pozen, Inc., Abbott Laboratories, Inc., Eli Lilly & Company, NPS, and Xcel

Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
					Pharmaceuticals; has received personal compensation in an editorial capacity for CurrentPain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Inc., Johnson & Johnson, Merck&Co., Inc., Pfizer, Inc., Allergan, Inc., and Abbott Laboratories, Inc. Dr. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan,Inc., Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil, Pfizer, Pozen, among other companies. Dr. Dodick has received personal compensation for activities with Allergan, Inc., GlaxoSmith-Kline, Inc., Pfizer, Inc., Endo Pharmaceuticals, Ortho-McNeil Pharmaceutical, Inc., Merck & Co., Inc., Medtronic, Neuralieve; has received personal compensation in an editorial capacity for Headache Currents; and has received research support from St. Jude, Allergan, Inc., Medtronic, Inc., National Institutes of Health, Mayo Clinic College of Medicine, and Advanced Bionics. Dr. Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer, Inc., and GlaxoSmithKline, Inc., and has received research support from Alzyer, AstraZeneca Pharmaceuticals, Inc., GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Precision, Division of Boston Scientific, Solvay S.A., and Vernalis. Dr. Ramadan has received personal compensation for activities with GlaxoSmithKline, Inc., Ortho- McNeil Neurologics, Inc., Eli Lilly & Company, Eisai, Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Pfizer, Inc., Merck & Co., Inc., Aradign Corp., Boehringer Ingelheim Pharmaceuticals and Map Pharmaceuticals; has received personal compensation in an editorial capacity for Web Alert; and has received research support from Ortho-McNeil Neurologics, Eli Lilly&Company, Pfizer, Inc., and the National Headache Ambassador Program. Dr. Mathew has received personal compensation for activities with Eisai. Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, UCB Pharma, Allergan, Johnson & Johnson, AstraZeneca, Pfizer, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Novartis, Endo, Pozen, Inc., Vernalis, Ortho-McNeil, Advanced Bionics; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Pfizer, Merck, Ortho-McNeil, Allergan, MedPointe Pharmaceuticals, Endo, UCB Pharma; has served as a consultant to Merck, GlaxoSmith-Kline, Pfizer, AstraZeneca, Allergan, Ortho-McNeil, Aradigm Corporation; and has received educational funding from GlaxoSmithKline. Dr. Bigal has received personal compensation for activities from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil,

Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
					UCB, AstraZeneca, Pfizer, Inc., and Advance PCS and has received research support from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, Pfizer, UCB, AstraZeneca, and Advance PCS. Dr. Saper has received honoraria for speaking from GlaxoSmithKline, Merck & Co., Inc., Abbott Laboratories, Inc., Elan Corporation, AstraZeneca Pharmaceuticals, Pfizer, Inc., Ortho-McNeil Pharmaceuticals, Bristol-Myers Squibb, Medtronic, Inc., Endo Pharmaceuticals, Advanced Bionics, Pozen, Inc., and Penwest Pharmaceuticals Co; has received personal compensation in an editorial capacity for Pain Watch and Migraine Monitor; holds stock in Pozen, Inc.; and has received research support from Novartis, Ortho-McNeil Pharmaceuticals, Merck & Co., Inc., GlaxoSmithKline, Allergan, Inc., Eisai, Inc., AstraZeneca Pharmaceuticals, Abbott, Advanced Bionics, Medtronic, Renovis, and Pozen, Inc.Dr. Ascher is an employee of Ortho-McNeil Janssen Scientific Affairs, LLC. Dr. Jordan is an employee of PriCara, a Unit of Ortho-McNeil, Inc. Drs. Greenberg and Joseph Hulihan are employees of Ortho-McNeil Neurologics.
Diener, 2007[33]	Industry	Not reported	Not reported	Yes	JC Van Oene, M Lahaye and S Schwalen are employess of Janssen-Cilag
Lainez, 2007[34]	Not reported	Yes	Yes	Yes	Miguel JA La´ inez has received personal compensation or research support from activities with Allergan, Inc., Almirall SA, GlaxoSmithKline, Inc Jansen Cilag, Inc., Menarini, Merck & Co., Inc, Medtronic and Pfizer Inc. Frederick Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals,., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer Inc, and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Advanced Bionics, Solvay S.A., and Vernalis. Joop Pfeil is a paid consultant for Janssen Pharmaceutica/J & J, Novartis, Sanofi-Aventis, Pfizer, Schering-Plough, Numico, Vitatron, Actelion Pharmaceuticals and Sankyo. S. Ascher is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. W.H. Olson is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. S. Schwalen is a full-time employee of Janssen-Cilag GmbH.
Diener, 2007[37]	Industry	Yes	Yes	Yes	Hans-Christoph Diener, Reto Agosti, Gianni Allais, Gennaro Bussone, Brendan Davies, Michel Lanteri-Minet, Mustafa Ertas, Uwe Reuter, Margarita Sanchez Del Rio, and Jean Schoenen have participated in clinical trials and advisory boards for Janssen-Cilag. Paul Bergmans, Susanne Schwalen, Joop van Oene are employees of Janssen-Cilag EMEA (Europe, Middle East, and Africa). Hans -Chirstoph Diener has received honoraria from Addex Pharmaceuticals, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid Pharmaceuticals, Böhringer Ingelheim, Bristol-Myers Squibb,

Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
					GlaxoSmithKline, Grünenthal, Janssen-Cilag, Eli Lilly, F Hoff mann-La Roche, 3M Medica, Merck Sharp and Dohme, Novartis Pharmaceuticals, Johnson and Johnson, Pierre Fabre, Pfi zer, Schaper and Brümmer, Sanofi -Aventis, and Weber and Weber, and fi nancial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfi zer.
Adelman, 2008[39]	Industry	Yes	Yes	Yes	James Adelman: Clinical Trials 1998–2006 (Ortho-McNeil Pharmaceuticals), Advisory Boards (Ortho-McNeil Pharmaceuticals), Speaker (Ortho-McNeil Pharmaceuticals); Frederick Freitag: Consultant, honoraria recipient (OrthoMcNeil Pharmaceuticals and Ortho-McNeil Neurologics), research grant recipient (Johnson and Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals, and Ortho-McNeil Neurologics); Miguel Lainez: grant/research recipient, consultant/scientific advisor, honoraria recipient (Allergan, Almirall Prodesfarma, Boehringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen Cilag, Johnson and Johnson, MSD, Novartis, Pierre Fabre, and Sanofi-Synthelabo).
Silberstein, 2009[40]	Industry	Yes	Yes	Yes	Stephen Silberstein has received personal compensation for activities with: Johnson & Johnson, GlaxoSmith-Kline, Merck, UCB Pharma, AstraZeneca, Pfizer, Allergan, Pozen, Abbott Laboratories., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial capacity for Current Pain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Allergan, and Abbott Laboratories. Richard B. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeill, Pfizer, and Pozen, among other companies. David W. Dodick has served as a consultant for GlaxoSmithKline, Merck, Allergan, Endo, Pfizer, Eli Lilly, Addex, Solvay, and Neuralieve and has received research support from Advanced Neurostimulation Systems, Medtronic, and St. Jude. Fred Freitag has received grants and research support from Advanced Bionics Corporation, Alzyer, AstraZeneca, CAPNIA, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Solvay, and Vernalis Pharmaceuticals.He has served as a consultant for Allergan,AstraZeneca,CAPNIA, Endo Pharmaceuticals, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, and Valeant Pharmaceuticals International. He has served on the speakers bureaus of AstraZeneca, GlaxoSmithKline, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Pfizer, and Valeant Pharmaceuticals International. Ninan Mathew has received personal compensation for activities involving continuing medical education and for advisory board participation from Ortho McNeil, Merck,

Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
					Allergan, GlaxoSmithKline, Endo, and Valiant. Jan Brandes has received grants, research support, or served as a consultant to Merck, GlaxoSmithKline, UCB Pharma, Pfizer, Allergan, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan, Novartis, Endo, Pozen,Vernalis, Ortho-McNeil, Advanced Bionics, MedPointe, and Aradigm. Marcelo E. Bigal is a full-time employee of Merck Research Laboratories.This manuscript was written during his tenure at the Albert Einstein College of Medicine.He has received, in the past, compensation from Ortho-McNeil Pharmaceutical,AstraZeneca, GlaxoSmithKline, Merck, Allergan, MAP, NMT, and Endo, among other pharmaceutical companies. Steve Ascher, Jacqueline D. Morein, and Pamela Wright are employees of Ortho-McNeil Janssen Scientific Affairs, LLC. Steven J. Greenberg is an employee of EMD Serono Inc.
Lipton, 2011[41]	Industry	Yes	Yes	Yes	Not reported, however, David Biondi, Steven Ascher, William Olson and Joseph Hulihan were from Ortho-McNeil Janssen Scientific Affairs, USA

Appendix Table D128. Risk of bias in randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Masking of the treatment status	Intention to treat analysis	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Storey, 2001[17]	Double-blind	No	Unclear	Yes (Topiramate group had no men and higher number of patients with concurrent preventative treatment), but the differences were not significant	Unclear	Low
Edwards, 2003[18]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
Silvestrini, 2003[19]	Double-blind	No	Unclear	Yes	Unclear	Low
Brandes, 2004[21]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Silberstein, 2004[22]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mei, 2004[23]	Double-blind	No	Unclear	Unclear	Unclear	Moderate
Bussone, 2005[24]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[26]	Double-blind	Yes	Unclear	Not adequate. Topiramate 200mg/day group has lower % of women and higher % of men as compared to other groups, but the differences were not significant (previously reported)	Unclear	Moderate
Mei, 2006[27]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[28]	Double-blind	Yes	Unclear	Not reported	Unclear	Moderate
Brandes, 2006[29]	Double-blind	Yes	Clearly adequate	Not adequate; the % of male patients was much lower in the topiramate100mg and 200mg groups, but the difference was not significant	Unclear	Moderate
Brandes, 2006[29]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[33]	Double-blind	Yes	Unclear	Not adequate (Mean Beck Depression Inventory scores were higher in placebo as compared to topiramate), but the differences were not significant	Unclear	Moderate
Lainez, 2007[34]	Double-blind	No	Unclear	Yes	Unclear	Low
Diener, 2007[37]	Double-blind	Yes	Unclear	Yes	Unclear	Moderate
Adelman, 2008[39]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2009[40]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Lipton, 2011[41]	Double-blind	Yes	Unclear	Yes	The study mentions the significance of the outcome: ≥50% and 75% reduction in headache days and migraine headache days, however, the results are not given	Low

Appendix Table D129. Treatment discontinuation due to adverse effects with topiramate vs. placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
Discontinued due to adverse events	Brandes, 2006[29] Moderate	100 mg/day	32/120 [30] 5/39 [10]	2.1 (0.9 to 5.0)	14.02	0.14 (0.01 to 0.27)	2.91	0.08 (0.01 to 0.14)
Withdrew due to adverse event	Silberstein, 2004[22] 200 Low	100 mg/day	24/128 [20] 4/40 [10]	1.9 (0.7 to 5.2)	10.66	0.09 (-0.02 to 0.20)	3.92	0.06 (0.00 to 0.13)
Discontinued due to limiting adverse events	Brandes, 2006[29] Low	100 mg/day	18/165 [10] 10/163 [10]	1.8 (0.8 to 3.7)	19.3	0.05 (-0.01 to 0.11)	13.87	0.05 (0.00 to 0.10)
Discontinued due to limiting adverse events	Lipton, 2011[41] Low	100 mg/day	21/188 [10] 18/197 [10]	1.2 (0.7 to 2.2)	29.82	0.02 (-0.04 to 0.08)	13.77	0.03 (-0.02 to 0.08)
Withdrew due to adverse events	Mei, 2004[23] Moderate	100 mg/day	3/58 [10] 2/57 [0]	1.5 (0.3 to 8.5)	3.46	0.02 (-0.06 to 0.09)	9.08	0.03 (-0.02 to 0.09)
Dropped out of the study due to adverse effects	Mei, 2006[27] Low	100 mg/day	9/30 [30] 6/20 [30]	1.0 (0.4 to 2.4)	14.23	0.00 (-0.26 to 0.26)	0.75	0.05 (-0.03 to 0.12)
Early discontinuation due to insufficient tolerability	Diener, 2007[37] Moderate	100mg/day	12/255 [0] 4/259 [0]	3.0 (1.0 to 9.3)	8.5	0.03 (0.00 to 0.06)	55.72	0.03 (0.01 to 0.06)
Early discontinuation due to insufficient tolerability	**Pooled**	100mg/day	**119/944 [10] 48/775 [10]**	**1.6 (1.1 to 2.2)**	**100**	**0.04 (0.01 to 0.06)**	**100**	**0.05 (0.01 to 0.09)**
P value for heterogeneity		100mg/day		p = 0.711		p = 0.673		
I-squared				I-squared 0.0%		I-squared 0.0%		
Discontinued due to adverse events	Brandes, 2006[29] Moderate	200mg/day	25/117 [20] 5/38 [10]	1.6 (0.7 to 3.9)	40.26	0.08 (-0.05 to 0.21)	21.52	0.12 (0.04 to 0.21)
Discontinued due to adverse events	Silberstein, 2006[28] Moderate	200mg/day	21/140 [20] 4/73 [10]	2.7 (1.0 to 7.7)	29.99	0.10 (0.02 to 0.17)	35.13	0.11 (0.05 to 0.18)
Discontinuations due to adverse events	Silberstein, 2006[26] Moderate	200mg/day	38/112 [30] 3/36 [10]	4.1 (1.3 to 12.4)	25.75	0.26 (0.13 to 0.38)	22.51	0.19 (0.10 to 0.28)
Discontinued due to adverse events	Edwards, 2003[18] Low	200mg/day	6/34 [20] 0/36 [0]	13.7 (0.8 to 235.0)	4.01	0.18 (0.04 to 0.31)	20.84	0.16 (0.07 to 0.25)
Discontinued due to adverse events	**Pooled**	200mg/day	**90/403 [20] 12/183 [10]**	**2.6 (1.5 to 4.6)**	**100**	**0.15 (0.07 to 0.22)**	**100**	**0.15 (0.07 to 0.22)**

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
P value for heterogeneity				p = 0.387		p = 0.137		
I-squared				I-squared = 1.1%		I-squared = 45.7%		
Discontinued due to adverse events	Brandes, 2006[29] Moderate	50mg/day	20/117 [20] 5/38 [10]	1.3 (0.5 to 3.2)	54.98	0.04 (-0.09 to 0.17)	46.98	0.07 (0.02 to 0.11)
Discontinuations due to adverse events	Silberstein, 2006[26] Moderate	50mg/day	21/117 [20] 4/38 [10]	1.7 (0.6 to 4.7)	45.02	0.07 (-0.05 to 0.19)	53.02	0.07 (0.03 to 0.11)
Discontinuations due to adverse events		50mg/day	41/234 [20] 8/76 [10]	1.5 (0.7 to 2.9)	100	0.06 (-0.03 to 0.15)	100	0.07 (-0.02 to 0.16)
P value for heterogeneity	Pooled	50mg/day		p = 0.694		p = 0.696		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Discontinued due to lack of efficacy	Brandes, 2006[29] Low	100 mg/day	21/165 [10] 30/163 [20]	0.7 (0.4 to 1.2)	24.33	-0.06 (-0.14 to 0.02)	15.94	-0.05 (-0.11 to 0.01)
Discontinued due to lack of efficacy	Lipton, 2011[41] Low	100 mg/day	6/188 [0] 8/197 [0]	0.8 (0.3 to 2.2)	9.82	-0.01 (-0.05 to 0.03)	37.56	-0.01 (-0.05 to 0.02)
Discontinued due to lack of efficacy	Brandes, 2006[29] Moderate	100 mg/day	11/120 [10] 7/39 [20]	0.5 (0.2 to 1.2)	12.73	-0.09 (-0.22 to 0.04)	6.8	-0.06 (-0.14 to 0.02)
Withdrew due to lack of efficacy	Silberstein, 2004[22] Low	100 mg/day	6/128 [0] 7/40 [20]	0.3 (0.1 to 0.8)	9.95	-0.13 (-0.25 to -0.01)	7.58	-0.08 (-0.16 to 0.00)
Withdrew due to lack of efficacy	Mei, 2004[23] Moderate	100 mg/day	17/58 [30] 13/57 [20]	1.3 (0.7 to 2.4)	19.88	0.07 (-0.10 to 0.23)	4.74	-0.02 (-0.10 to 0.07)
Insufficient efficacy resulting in discontinuation	Diener, 2007[37] Moderate	100mg/day	19/255 [10] 33/259 [10]	0.6 (0.3 to 1.0)	23.29	-0.05 (-0.11 to 0.00)	27.39	-0.05 (-0.10 to -0.01)
Discontinued due to lack of efficacy	Pooled	100mg/day	80/914 [10] 98/755 [10]	0.7 (0.5 to 1.0)	100	-0.04 (-0.08 to 0.00)	100	-0.05 (-0.09 to 0.00)
P value for heterogeneity				p = 0.160		p = 0.224		
I-squared				I-squared = 37.0%		I-squared = 28.1%		

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
Discontinued due to lack of efficacy	Silberstein, 2006[28] Moderate	200mg/day	4/140 [0] 2/73 [0]	1.0 (0.2 to 5.6)	11.68	0.00 (-0.05 to 0.05)	48.06	-0.01 (-0.05 to 0.03)
Discontinued due to lack of efficacy	Edwards, 2003[18] Low	200mg/day	1/34 [0] 4/36 [10]	0.3 (0.0 to 2.3)	7.14	-0.08 (-0.20 to 0.04)	19.69	-0.07 (-0.14 to 0.00)
Discontinued due to lack of efficacy	Brandes, 2006[29] Moderate	200mg/day	12/117 [10] 7/38 [20]	0.6 (0.2 to 1.3)	44.51	-0.08 (-0.22 to 0.05)	16.06	-0.07 (-0.14 to 0.01)
Withdrew due to lack of efficacy	Silberstein, 2004[22] Low	200mg/day	8/117 [10] 7/37 [20]	0.4 (0.1 to 0.9)	36.67	-0.12 (-0.26 to 0.01)	16.19	-0.08 (-0.15 to 0.00)
Discontinued due to lack of efficacy	Pooled	200mg/day	25/408 [10] 19/184 [10]	0.5 (0.3 to 0.9)	100	-0.05 (-0.11 to 0.01)	100	-0.06 (-0.12 to 0.01)
P value for heterogeneity				p = 0.663		p = 0.191		
I-squared				I-squared = 0.0%		I-squared = 36.8%		
Discontinued due to lack of efficacy	Brandes, 2006[29] Moderate	50mg/day	15/117 [10] 7/38 [20]	0.7 (0.3 to 1.6)	54.5	-0.06 (-0.19 to 0.08)	47.06	-0.07 (-0.13 to -0.01)
Withdrew due to lack of efficacy	Silberstein, 2004[22] Low	50mg/day	10/125 [10] 7/40 [20]	0.4 (0.2 to 1.1)	45.5	-0.10 (-0.23 to 0.03)	52.94	-0.08 (-0.14 to -0.02)
Discontinued due to lack of efficacy	Pooled	50mg/day	25/242 [10] 14/77 [20]	0.6 (0.3 to 1.0)	100	-0.08 (-0.17 to 0.02)	100	-0.08 (-0.18 to 0.03)
P value for heterogeneity		50mg/day		p = 0.472		p = 0.652		
I-squared				I-squared = 0.0% (0.0 to 0.0)		I-squared = 0.0%		0.00
Treatment-limiting: Dizziness leading to discontinuation	Lainez, 2007[34] Low	100 mg/day	8/391 [0] 6/383 [0]	1.3 (0.5 to 3.7)	49.34	0.01 (-0.01 to 0.02)	42.17	0.00 (-0.01 to 0.02)
Dropout due to dizziness	Mei, 2006[27] Low	100 mg/day	0/30 [0] 2/20 [10]	0.1 (0.0 to 2.7)	6.09	-0.10 (-0.25 to 0.05)	0.7	-0.01 (-0.05 to 0.03)
Dizziness leading to withdrawal	Adelman, 2008[39] Risk of bias Low	200mg/day	13/514 [0] 3/202 [0]	1.7 (0.5 to 5.9)	35.05	0.01 (-0.01 to 0.03)	31.87	0.01 (-0.01 to 0.03)
Dizziness leading to withdrawal	Adelman, 2008[39] Low	50mg/day	2/235 [0] 1/92 [0]	0.8 (0.1 to 8.5)	9.52	0.00 (-0.03 to 0.02)	25.26	-0.01 (-0.03 to 0.02)
Dizziness leading to	Pooled	50-200mg/day	23/1170 [0]	1.2 (0.6 to 2.5)	100	0.00 (-0.01 to 0.02)	100	0.00 (-0.02 to 0.02)

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
withdrawal			13/697 [0]					
P value for heterogeneity				p = 0.477		p = 0.463		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Treatment-limiting: Insomnia leading to discontinuation	Lainez, 2007[34] Low	100 mg/day	13/391 [0] 4/383 [0]	3.2 (1.0 to 9.7)	51.01	0.02 (0.00 to 0.04)	37.21	0.02 (0.00 to 0.04)
Dropout due to insomnia	Mei, 2006[27] Low	100 mg/day	0/30 [0] 1/20 [10]	0.2 (0.0 to 5.3)	6.34	-0.05 (-0.17 to 0.07)	1.11	0.00 (-0.04 to 0.04)
Insomnia leading to withdrawal	Adelman, 2008[39] Low	200mg/day	13/514 [0] 2/202 [0]	2.5 (0.6 to 11.2)	28.79	0.02 (0.00 to 0.04)	41.9	0.01 (-0.01 to 0.03)
Insomnia leading to withdrawal	Adelman, 2008[39] Low	50mg/day	5/235 [0] 1/92 [0]	2.0 (0.2 to 16.5)	13.85	0.01 (-0.02 to 0.04)	19.78	0.01 (-0.01 to 0.03)
Insomnia leading to withdrawal	**Pooled**	**50-200mg/day**	**31/1170 [0] 8/697 [0]**	**2.4 (1.1 to 5.2)**	**100**	**0.02 (0.00 to 0.03)**	**100**	**0.01 (-0.01 to 0.03)**
P value for heterogeneity				p = 0.485		p = 0.623		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Language problems leading to withdrawal	Adelman, 2008[39] Low	100 mg/day	6/386 [0] 1/151 [0]	2.4 (0.3 to 19.5)	32.44	0.01 (-0.01 to 0.03)	33.65	0.01 (0.00 to 0.03)
Language problems leading to withdrawal	Adelman, 2008[39] Low	200mg/day	10/514 [0] 1/202 [0]	3.9 (0.5 to 30.5)	34.36	0.02 (0.00 to 0.03)	45.22	0.02 (0.00 to 0.03)
Language problems leading to withdrawal	Adelman, 2008[39] Low	50mg/day	4/235 [0] 0/92 [0]	3.5 (0.2 to 65.2)	17.01	0.02 (-0.01 to 0.04)	20.34	0.01 (0.00 to 0.03)
Dropout due to speech difficulties	Mei, 2006[27] Low	100 mg/day	2/30 [10] 0/20 [0]	3.4 (0.2 to 67.0)	16.19	0.07 (-0.05 to 0.18)	0.79	0.02 (0.00 to 0.04)
Language problems leading to withdrawal	**Pooled**	**50-200mg/day**	22/1165 [1.9] 2/465 [0.4]	**3.2 (1.0 to 10.6)**	**100**	**0.01 (0.00 to 0.02)**	**100**	**0.02 (0.00 to 0.03)**
P value for heterogeneity				p = 0.989		p = 0.762		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Dropout due to paresthesia	Mei, 2006[27] Low	100 mg/day	4/30 [10] 0/20 [0]	6.1 (0.3 to 107.4)	8.35	0.13 (-0.01 to 0.27)	2.94	0.08 (0.03 to 0.13)

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
Dropout due to paresthesia	Mei, 2004[23] Moderate	100 mg/day	5/58 [10] 0/57 [0]	10.8 (0.6 to 191.2)	8.33	0.09 (0.01 to 0.16)	8.34	0.08 (0.03 to 0.12)
Treatment-limiting: Paresthesia leading to discontinuation	Lainez, 2007[34] Low	100 mg/day	31/391 [10] 3/383 [0]	10.1 (3.1 to 32.8)	49.65	0.07 (0.04 to 0.10)	29.32	0.07 (0.05 to 0.10)
Paresthesia leading to withdrawal	Adelman, 2008[39] Low	200mg/day	37/514 [10] 1/202 [0]	14.5 (2.0 to 104.7)	17.54	0.07 (0.04 to 0.09)	32.43	0.07 (0.04 to 0.09)
Paresthesia leading to withdrawal	Adelman, 2008[39] Low	50mg/day	8/235 [0] 1/92 [0]	3.2 (0.4 to 25.0)	16.12	0.02 (-0.01 to 0.06)	26.98	0.04 (0.01 to 0.06)
Paresthesia leading to withdrawal	**Pooled**	**50-200mg/day**	**85/1228 [10] 5/754 [0]**	**8.6 (3.8 to 19.7)**	**100**	**0.06 (0.04 to 0.09)**	**100**	**0.07 (0.04 to 0.09)**
P value for heterogeneity				p = 0.858		p = 0.102		
I-squared				I-squared = 0.0%		I-squared = 48.2%		
Dropout due to somnolence	Mei, 2004[23] Moderate	100 mg/day	2/58 [0] 1/57 [0]	2.0 (0.2 to 21.1)	10.11	0.02 (-0.04 to 0.08)	6.28	0.00 (-0.01 to 0.02)
Somnolence leading to withdrawal	Adelman, 2008[39] Low	100 mg/day	7/386 [0] 3/151 [0]	0.9 (0.2 to 3.5)	31.7	0.00 (-0.03 to 0.02)	31.76	0.00 (-0.01 to 0.02)
Somnolence leading to withdrawal	Adelman, 2008[39] Low	200mg/day	10/514 [0] 4/202 [0]	1.0 (0.3 to 3.1)	43.16	0.00 (-0.02 to 0.02)	41.34	0.00 (-0.01 to 0.02)
Somnolence leading to withdrawal	Adelman, 2008[39] Low	50mg/day	2/235 [0] 2/92 [0]	0.4 (0.1 to 2.7)	15.03	-0.01 (-0.05 to 0.02)	20.62	0.00 (-0.02 to 0.01)
Somnolence leading to withdrawal	Pooled	50-200mg/day	21/1193 [0] 9/502 [0]	0.9 (0.4 to 1.9)	100	0.00 (-0.02 to 0.01)	100	0.00 (-0.02 to 0.02)
P value for heterogeneity				p = 0.767		p = 0.825		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Dropout due to alteration of taste	Mei, 2006[27] Low	100 mg/day	2/30 [10] 0/20 [0]	3.4 (0.2 to 67.0)	20.47	0.07 (-0.05 to 0.18)	0.47	0.02 (-0.01 to 0.04)
Dropout due to alteration of taste	Mei, 2004[23] Moderate	100 mg/day	1/58 [0] 0/57 [0]	2.9 (0.1 to 70.9)	18.04	0.02 (-0.03 to 0.06)	2.89	0.01 (-0.01 to 0.03)
Taste perversion leading to withdrawal	Adelman, 2008[39] Low	100 mg/day	4/386 [0] 0/151 [0]	3.5 (0.2 to 65.3)	21.46	0.01 (0.00 to 0.02)	31.99	0.01 (0.00 to 0.02)
Taste perversion leading to withdrawal	Adelman, 2008[39] Low	200mg/day	6/514 [0] 0/202 [0]	5.1 (0.3 to 90.5)	22.12	0.01 (0.00 to 0.02)	45.18	0.01 (0.00 to 0.02)

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
Taste perversion leading to withdrawal	Adelman, 2008[39] Low	50mg/day	1/235 [0] 0/92 [0]	1.2 (0.0 to 28.8)	17.91	0.00 (-0.01 to 0.02)	19.47	0.01 (-0.01 to 0.02)
Taste perversion leading to withdrawal	Pooled	50-200mg/day	14/1223 [0] 0/522 [0]	3.0 (0.8 to 11.7)	100	0.01 (0.00 to 0.02)	100	0.01 (0.00 to 0.02)
P value for heterogeneity				p = 0.976		p = 0.830		
I-squared				I-squared = 0.0%		I-squared = 0.0%		
Discontinued	Lipton, 2011[41] Low	100 mg/day	69/188 [40] 86/197 [40]	0.8 (0.7 to 1.1)	14.21	-0.07 (-0.17 to 0.03)	11.86	-0.05 (-0.13 to 0.04)
Discontinued prematurely	Silberstein, 2007[30] Low	100 mg/day	73/165 [40] 73/163 [40]	1.0 (0.8 to 1.3)	14.38	-0.01 (-0.11 to 0.10)	10.97	0.00 (-0.09 to 0.09)
Withdrew	Adelman, 2008[39] Low	100 mg/day	146/386 [40] 52/151 [30]	1.1 (0.9 to 1.4)	13.85	0.03 (-0.06 to 0.12)	12.59	0.03 (-0.05 to 0.11)
Withdrew	Mei, 2004[23] Moderate	100 mg/day	23/58 [40] 20/57 [40]	1.1 (0.7 to 1.8)	7.24	0.05 (-0.13 to 0.22)	6.36	0.03 (-0.09 to 0.16)
Early discontinuation	Diener, 2007[37] Moderate	100mg/day	44/255 [20] 51/259 [20]	0.9 (0.6 to 1.3)	9.99	-0.02 (-0.09 to 0.04)	14.85	-0.02 (-0.08 to 0.05)
Discontinuations	Diener, 2007[33] Moderate	200mg/day	8/32 [30] 13/27 [50]	0.5 (0.3 to 1.1)	3.9	-0.23 (-0.47 to 0.01)	4.04	-0.06 (-0.20 to 0.08)
Discontinued	Silberstein, 2006[28] Moderate	200mg/day	43/140 [30] 13/73 [20]	1.7 (1.0 to 3.0)	5.86	0.13 (0.01 to 0.25)	10.23	0.10 (0.00 to 0.19)
Discontinued	Edwards, 2003[18] Low	200mg/day	10/34 [30] 8/36 [20]	1.3 (0.6 to 3.0)	3.22	0.07 (-0.13 to 0.28)	5.17	0.04 (-0.09 to 0.17)
Withdrew	Adelman, 2008[39] Low	200mg/day	239/514 [50] 70/202 [30]	1.3 (1.1 to 1.7)	15.66	0.12 (0.04 to 0.20)	13.71	0.10 (0.03 to 0.17)
Withdrew	Adelman, 2008[39] Low	50mg/day	108/235 [50] 32/92 [30]	1.3 (1.0 to 1.8)	11.68	0.11 (-0.01 to 0.23)	10.23	0.08 (-0.01 to 0.18)
Early discontinuation	Pooled	50-200mg/day	755/2007 [40] 405/1257 [30]	1.1 (0.9 to 1.3)	100	0.03 (-0.03 to 0.08)	100	0.03 (-0.03 to 0.09)
P value for heterogeneity				p = 0.030		p = 0.012		
I-squared				I-squared =		I-squared = 57.6%		

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
				51.4%				
Treatment-limiting: Any cognitive symptom (including confusion, difficulty with concentration/attention, and difficulty with memory) leading to discontinuation	Lainez, 2007[34] Low	100 mg/day	28/391 [10] 8/383 [0]	3.4 (1.6 to 7.4)	50.57	0.05 (0.02 to 0.08)	21.01	0.05 (0.02 to 0.08)
Dropout due to cognitive difficulties	Mei, 2004[23] Moderate	100 mg/day	7/58 [10] 0/57 [0]	14.7 (0.9 to 252.3)	6.42	0.12 (0.03 to 0.21)	6.82	0.07 (0.02 to 0.13)
Confusion leading to withdrawal	Lipton, 2011[41] Low	100 mg/day	10/188 [10] 3/197 [0]	3.5 (1.0 to 12.5)	25.99	0.04 (0.00 to 0.07)	18.44	0.04 (0.01 to 0.07)
Dropout due to difficulty concentrating	Mei, 2006[27] Low	100 mg/day	0/30 [0] 1/20 [10]	0.2 (0.0 to 5.3)	5.27	-0.05 (-0.17 to 0.07)	4.23	0.01 (-0.05 to 0.08)
Difficulty with concentration/attention leading to withdrawal	Adelman, 2008[39] Low	200mg/day	24/514 [0] 0/202 [0]	19.2 (1.2 to 314.5)	6.61	0.05 (0.03 to 0.07)	24.48	0.04 (0.03 to 0.06)
Difficulty with concentration/attention leading to withdrawal	Adelman, 2008[39] Low	50mg/day	1/235 [0] 0/92 [0]	1.2 (0.0 to 28.8)	5.14	0.00 (-0.01 to 0.02)	25.02	0.00 (-0.01 to 0.02)
Difficulty with concentration/attention leading to withdrawal	**Pooled**	**50-200mg/day**	**70/1416 [0] 13/951 [0]**	**3.5 (1.7 to 7.3)**	**100**	**0.04 (0.01 to 0.06)**	**100**	**0.04 (0.01 to 0.07)**
P value for heterogeneity				p = 0.330		p = 0.002		0.00
I-squared				I-squared = 13.2%		I-squared = 73.0%		0.00
Fatigue leading to withdrawal	Mei, 2004[23] Moderate	100 mg/day	0/58 [0] 1/57 [0]	0.3 (0.0 to 7.9)	38.65	-0.02 (-0.07 to 0.03)	11.72	0.00 (-0.03 to 0.03)
Fatigue leading to withdrawal	Lainez, 2007[34] Low	100 mg/day	18/391 [0] 3/383 [0]	5.9 (1.7 to 19.8)	9.41	0.04 (0.02 to 0.06)	31.88	0.03 (0.01 to 0.05)
Fatigue leading to withdrawal	Mei, 2006[27] Low	100 mg/day	1/30 [0] 1/20 [10]	0.7 (0.0 to 10.1)	29.59	-0.02 (-0.13 to 0.10)	2.3	0.01 (-0.03 to 0.06)
Fatigue leading to withdrawal	Adelman, 2008[39] Low	200mg/day	24/514 [0] 2/202 [0]	4.7 (1.1 to 19.8)	15.4	0.04 (0.01 to 0.06)	31.57	0.03 (0.01 to 0.05)

Appendix Table 129. Treatment discontinuation due to adverse effects with topiramate versus placebo (pooled results from randomized controlled clinical trials that examined migraine prevention in adults) (continued)

Definition of the outcome	Reference Risk of bias	Daily dose	Events/ randomized [rate, %] with drugs and placebo	Relative risk (95% CI)	Weight, random effects, inverse variance	Absolute risk difference (95% CI)	Weight, Random effects, inverse variance	Absolute risk difference Maximum likelihood
Fatigue leading to withdrawal	Adelman, 2008[39] Low	50mg/day	7/235 [0] 1/92 [0]	2.7 (0.3 to 22.0)	100	0.02 (-0.01 to 0.05)	22.52	0.02 (0.00 to 0.04)
Fatigue leading to withdrawal	**Pooled**	**50-200mg/day**	**50/1228 [0] 8/754 [0]**	**3.3 (1.4 to 7.7)**		**0.03 (0.01 to 0.04)**	**100**	**0.02 (0.00 to 0.04)**
P value for heterogeneity				p = 0.344 (0.0 to 0.0)		p = 0.209		
I-squared				I-squared 10.8%		I-squared = 31.8%		

Bold - significant differences at 95% CI
CI – confidence interval

Appendix Table D130. Strength of evidence of treatment discontinuation due to adverse effects with topiramate vs. placebo in adults with migraine (based on pooled results from randomized controlled clinical trials)

Definition of the outcome	Dose of drug	Reference, total sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Discontinued due to adverse events	100mg/day	1719	Moderate	Yes	Yes	Yes	Moderate
		Brandes, 2006[29]	Moderate				
		Silberstein, 2004[22]	Low				
		Silberstein, 2007[30]	Low				
		Lipton, 2011[41]	Low				
		Mei, 2004[23]	Moderate				
		Mei, 2006[27]	Low				
		Diener, 2007[37]	Moderate				
Discontinued due to adverse events	200mg/day	586	Moderate	Yes	Yes	No	Low
		Brandes, 2006[29]	Moderate				
		Silberstein, 2006[28]	Moderate				
		Silberstein, 2006[26]	Moderate				
		Edwards, 2003[18]	Low				
Discontinuations due to adverse events	50mg/day	310	Moderate	Yes	Yes	No	Low
		Brandes, 2006[29]	Moderate				
		Silberstein, 2006[26]	Moderate				
Discontinued due to lack of efficacy	200mg/day	592	Moderate	Yes	Yes	No	Low
		Brandes, 2006[29]	Low				
		Lipton, 2011[41]	Low				
		Brandes, 2006[29]	Moderate				
		Silberstein, 2004[22]	Low				
		Mei, 2004[23]	Moderate				
		Diener, 2007[37]	Moderate				
		1669	Moderate	Yes	Yes	Yes	Moderate
		Silberstein, 2006[28]	Moderate				
		Edwards, 2003[18]	Low				
		Brandes, 2006[29]	Moderate				

Appendix Table 130. Strength of evidence of treatment discontinuation due to adverse effects with topiramate versus placebo in adults with migraine (based on pooled results from randomized controlled clinical trials) (continued)

Definition of the outcome	Dose of drug	Reference, total sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
		Silberstein, 2004[22]	Low				
Discontinued due to lack of efficacy	50mg/day	319	Moderate	Yes	Yes	No	Low
		Brandes, 2006[29]	Moderate				
		Silberstein, 2004[22]	Low				
Dizziness leading to withdrawal	50-200mg/day	1867	Low	Yes	Yes	No	Moderate
		Lainez, 2007[34]	Low				
		Mei, 2006[27]	Low				
		Adelman, 2008[39]	Low				
Fatigue leading to withdrawal	50-200mg/day	1982	Low	Yes	Yes	Yes	High
		Mei, 2004[23]	Moderate				
		Lainez, 2007[34]	Low				
		Mei, 2006[27]	Low				
		Adelman, 2008[39]	Low				
Insomnia leading to withdrawal	50-200mg/day	1867	Low	Yes	Yes	No	Moderate
		Lainez, 2007[34]	Low				
		Mei, 2006[27]	Low				
		Adelman, 2008[39]	Low				
Language problems leading to withdrawal	50-200mg/day	1630	Low	Yes	Yes	No	Moderate
		Adelman, 2008[39]	Low				
		Mei, 2006[27]	Low				
Paresthesia leading to withdrawal	50-200mg/day	1982	Low	Yes	Yes	No	Moderate
		Mei, 2006[27]	Low				
		Mei, 2004[23]	Moderate				
		Lainez, 2007[34]	Low				
		Adelman, 2008[39]	Low				
Somnolence leading to withdrawal	50-200mg/day	1695	Low	Yes	Yes	No	Moderate
		Mei, 2004[23]	Moderate				
		Adelman, 2008[39]	Low				

Appendix Table 130. Strength of evidence of treatment discontinuation due to adverse effects with topiramate versus placebo in adults with migraine (based on pooled results from randomized controlled clinical trials) (continued)

Definition of the outcome	Dose of drug	Reference, total sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Taste perversion leading to withdrawal	50-200mg/day	1745	Low	Yes	Yes	No	Moderate
		Mei, 2006[27]	Low				
		Mei, 2004[23]	Moderate				
		Adelman, 2008[39]	Low				
Early discontinuation	50-200mg/day	3264	Low	Yes	No	No	Low
		Lipton, 2011[41]	Low				
		Silberstein, 2007[30]	Low				
		Adelman, 2008[39]	Low				
		Mei, 2004[23]	Moderate				
		Diener, 2007[37]	Moderate				
		Diener, 2007[33]	Moderate				
		Silberstein, 2006[28]	Moderate				
		Edwards, 2003[18]	Low				
		Adelman, 2008[39]	Low				
Dropout due to cognitive difficulties	50-200mg/day	2367	Low	Yes	Yes	Yes	High
		Lainez, 2007[34]	Low				
		Mei, 2004[23]	Moderate				
		Lipton, 2011[41]	Low				
		Mei, 2006[27]	Low				
		Adelman, 2008[39]	Low				

Appendix Table D131. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults[39]

Outcome, Daily dose	Events/randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm 1 person (95% CI) Attributable events per 1000 treated (95% CI)
Abdominal pain leading to withdrawal 50mg/day	5/235 [1/92]	2.1 [0.9]	1.8 (0.3 to 10.7)	0.01 (-0.02 to 0.04)	
Abdominal pain leading to withdrawal 100mg/day	3/386 [1/151]	0.8 [0.9]	1.2 (0.1 to 10.4)	0.00 (-0.01 to 0.02)	
Abdominal pain leading to withdrawal 200mg/day	12/514 [2/202]	2.3 [0.9]	2.0 (0.6 to 6.5)	0.01 (-0.01 to 0.03)	
Abnormal vision leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.0]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	
Abnormal vision leading to withdrawal 100 mg/day	3/386 [0/151]	0.8 [0.0]	4.0 (0.3 to 50.3)	0.01 (-0.01 to 0.02)	
Abnormal vision leading to withdrawal 200mg/day	5/514 [0/202]	1.0 [0.0]	4.1 (0.6 to 28.6)	0.01 (0.00 to 0.02)	
Anorexia leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.5]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	
Anorexia leading to withdrawal 100 mg/day	8/386 [1/151]	2.1 [0.5]	2.4 (0.5 to 10.2)	0.01 (-0.01 to 0.03)	
Anorexia leading to withdrawal 200mg/day	**14/514 [1/202]**	**2.7 [0.5]**	**3.0 (1.0 to 9.2)**	**0.02 (0.01 to 0.04)**	**NNT 45 (25 to 192) Attributable events 22 (5 to 39)**
Anxiety leading to withdrawal 50mg/day	3/235 [0/92]	1.3 [0.0]	4.1 (0.3 to 50.6)	0.01 (-0.01 to 0.03)	
Anxiety leading to withdrawal 100 mg/day	**8/386 [0/151]**	**2.1 [0.2]**	**4.1 (0.9 to 19.3)**	**0.02 (0.00 to 0.04)**	**NNT 48 (26 to 284) Attributable events 21 (4 to 38)**
Anxiety leading to withdrawal 200mg/day	**9/514 [0/202]**	**1.8 [0.2]**	**4.1 (0.9 to 17.6)**	**0.02 (0.00 to 0.03)**	**NNT 57 (32 to 249) Attributable events 18 (4 to 31)**
Arthralgia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Arthralgia leading to withdrawal 100 mg/day	2/386 [0/151]	0.5 [0.0]	4.0 (0.2 to 88.2)	0.01 (-0.01 to 0.02)	
Arthralgia leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	
Back pain leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.0]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	
Back pain leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	
Depression leading to withdrawal	1/235	0.4 [0.7]	0.3 (0.0 to 7.5)	-0.01 (-0.03 to 0.02)	

Appendix Table 131. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults[38] (continued)

Outcome, Daily dose	Events/randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm 1 person (95% CI) Attributable events per 1000 treated (95% CI)
50mg/day	[1/92]				
Depression leading to withdrawal 100 mg/day	3/386 [1/151]	0.8 [0.7]	1.2 (0.1 to 10.4)	0.00 (-0.01 to 0.02)	
Depression leading to withdrawal 200mg/day	**14/514 [1/202]**	**2.7 [0.7]**	**3.0 (0.9 to 9.2)**	**0.02 (0.01 to 0.04)**	**NNT 45 (25 to 194) Attributable events 22 (5 to 40)**
Diarrhea leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.5]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	
Diarrhea leading to withdrawal 100 mg/day	6/386 [1/151]	1.6 [0.5]	2.0 (0.4 to 10.5)	0.01 (-0.01 to 0.03)	
Diarrhea leading to withdrawal 200mg/day	10/514 [1/202]	1.9 [0.5]	2.6 (0.7 to 9.8)	0.01 (0.00 to 0.03)	
Dry mouth leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.5]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Dry mouth leading to withdrawal 100 mg/day	2/386 [1/151]	0.5 [0.5]	0.8 (0.1 to 9.6)	0.00 (-0.02 to 0.01)	
Dry mouth leading to withdrawal 200mg/day	5/514 [1/202]	1.0 [0.5]	1.8 (0.3 to 10.6)	0.00 (-0.01 to 0.02)	
Dyspepsia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.2]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Dyspepsia leading to withdrawal 100 mg/day	4/386 [0/151]	1.0 [0.0]	4.1 (0.5 to 36.1)	0.01 (0.00 to 0.02)	
Dyspepsia leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	
Hypesthesia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.2]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Hypesthesia leading to withdrawal 100 mg/day	**7/386 [0/151]**	**1.8 [0.2]**	**4.1 (0.8 to 21.4)**	**0.02 (0.00 to 0.03)**	**NNT 55 (29 to 603) Attributable events 18 (2 to 35)**
Hypesthesia leading to withdrawal 200mg/day	**12/514 [0/202]**	**2.3 [0.2]**	**4.1 (1.2 to 14.6)**	**0.02 (0.01 to 0.04)**	**NNT 43 (26 to 119) Attributable events 23 (8 to 38)**
Injury leading to withdrawal 100 mg/day	1/386 [0/151]	0.3 [0.0]	4.0 (0.1 to 314.4)	0.00 (-0.01 to 0.01)	
Mood problems leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.2]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	
Mood problems leading to withdrawal 100 mg/day	5/386 [0/151]	1.3 [0.2]	4.1 (0.6 to 28.7)	0.01 (0.00 to 0.03)	
Mood problems leading to withdrawal	**10/514 [0/202]**	**1.9 [0.2]**	**4.1 (1.0 to 16.4)**	**0.02 (0.01 to 0.03)**	**NNT 51 (30 to 183) Attributable events 20 (6 to**

Appendix Table 131. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults[38] (continued)

Outcome, Daily dose	Events/randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm 1 person (95% CI) Attributable events per 1000 treated (95% CI)
200mg/day					**34)**
Nausea leading to withdrawal 50mg/day	7/235 [1/92]	3.0 [1.1]	2.2 (0.5 to 10.5)	0.02 (-0.01 to 0.05)	
Nausea leading to withdrawal 100 mg/day	9/386 [2/151]	2.3 [1.1]	1.7 (0.4 to 6.2)	0.01 (-0.01 to 0.03)	
Nausea leading to withdrawal 200mg/day	**29/514 [2/202]**	**5.6 [1.1]**	**3.1 (1.4 to 6.8)**	**0.05 (0.02 to 0.07)**	**NNT 22 (14 to 45) Attributable events 47 (23 to 71)**
Pharyngitis leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Pharyngitis leading to withdrawal 100 mg/day	2/386 [0/151]	0.5 [0.0]	4.0 (0.2 to 88.2)	0.01 (-0.01 to 0.02)	
Sinusitis leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	
Weight loss leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	
Weight loss leading to withdrawal 100 mg/day	4/386 [0/151]	1.0 [0.0]	4.1 (0.5 to 36.1)	0.01 (0.00 to 0.02)	
Weight loss leading to withdrawal 200mg/day	6/514 [0/202]	1.2 [0.0]	4.1 (0.7 to 24.2)	0.01 (0.00 to 0.02)	

Bold - significant at 95% confidence limit; CI – confidence interval

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Serious adverse effects	Silberstein, 2009[40]	100	26/165 [18/163]	15.8 [11.0]	1.5 (0.8 to 2.8)	0.05 (-0.03 to 0.12)	32.95
Serious adverse effects	Diener, 2007[37]	100	7/255 [10/259]	2.7 [3.9]	0.7 (0.3 to 1.9)	-0.01 (-0.04 to 0.02)	67.05
Serious adverse effects	Pooled	100	33/420 [28/422]	7.9 [6.6]	1.2 (0.7 to 2.0)	0.01 (-0.05 to 0.06)	100
Abdominal pain	Adelman, 2008[39]	100	25/386 [8/151]	6.5 [5.2]	1.2 (0.6 to 2.7)	0.01 (-0.03 to 0.06)	16.82
Abdominal pain	Diener, 2007[37]	100	6/255 [5/259]	2.4 [1.9]	1.2 (0.4 to 4.0)	0.00 (-0.02 to 0.03)	49.99
Abdominal pain	Adelman, 2008[39]	200	35/514 [10/202]	6.8 [5.2]	1.4 (0.7 to 2.7)	0.02 (-0.02 to 0.06)	22.75
Abdominal pain	Adelman, 2008[39]	50	13/235 [5/92]	5.5 [5.2]	1.0 (0.4 to 2.9)	0.00 (-0.05 to 0.06)	10.45
Abdominal pain	Pooled	All doses	79/1390 [28/704]	5.7 [4.0]	1.2 (0.8 to 1.9)	0.01 (-0.01 to 0.03)	100
Any adverse event	Adelman, 2008[39]	100	349/386 [114/151]	90.4 [75.1]	3.6 (2.1 to 6.2)	0.15 (0.08 to 0.23)	14.04
Any adverse event	Silberstein, 2009[40]	100	132/165 [113/163]	80.0 [69.3]	1.8 (1.1 to 2.9)	0.11 (0.01 to 0.20)	12.81
Any adverse event	Lipton, 2011[41]	100	10/188 [13/197]	5.3 [6.6]	0.8 (0.3 to 1.8)	-0.01 (-0.06 to 0.03)	15.66
Any adverse event	Diener, 2007[37]	100	173/255 [151/259]	67.8 [58.3]	1.5 (1.1 to 2.2)	0.10 (0.01 to 0.18)	13.51
Any adverse event	Silberstein, 2006[28]	200	126/140 [51/73]	90.0 [69.9]	4.2 (2.0 to 8.8)	0.20 (0.09 to 0.32)	11.29
Any adverse event	Adelman, 2008[39]	200	470/514 [151/202]	91.4 [75.1]	4.2 (2.6 to 6.7)	0.16 (0.10 to 0.23)	14.69
Any adverse event	Diener, 2007[33]	50 to 200	24/32 [10/27]	75.0 [37.0]	4.6 (1.7 to 12.9)	0.38 (0.14 to 0.62)	5.53
Any adverse event	Adelman, 2008[39]	50	204/235 [69/92]	86.8 [75.1]	2.3 (1.2 to 4.5)	0.12 (0.02 to 0.22)	12.47
Any adverse event	Pooled	All doses	**1488/1915 [672/1164]**	**77.7 [57.7]**	**2.3 (1.9 to 2.8)**	**0.13 (0.06 to 0.20)**	**100**

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Anorexia	Bussone, 2005[24]	100	56/386 [22/372]	14.5 [5.9]	2.5 (1.6 to 4.0)	0.09 (0.04 to 0.13)	14.14
Anorexia	Mei, 2006[27]	100	9/30 [0/20]	30.0 [0.0]	7.3 (1.7 to 31.5)	0.30 (0.13 to 0.48)	2.71
Anorexia	Silberstein, 2007[30]	100	8/165 [9/163]	5.0 [5.6]	0.9 (0.3 to 2.3)	-0.01 (-0.06 to 0.04)	13.19
Anorexia	Lipton, 2011[41]	100	15/188 [5/197]	8.0 [2.5]	3.0 (1.2 to 7.4)	0.05 (0.01 to 0.10)	13.79
Anorexia	Diener, 2007[37]	100	13/255 [9/259]	5.1 [3.5]	1.5 (0.6 to 3.5)	0.02 (-0.02 to 0.05)	15.46
Anorexia	Storey, 2001[17]	200	4/19 [1/21]	21.1 [4.8]	4.3 (0.7 to 27.2)	0.16 (-0.04 to 0.37)	2.06
Anorexia	Silberstein, 2006[28]	200	19/140 [5/73]	13.6 [6.8]	2.0 (0.8 to 4.8)	0.07 (-0.01 to 0.15)	8.33
Anorexia	Adelman, 2008[39]	200	72/514 [12/202]	14.0 [6.1]	2.2 (1.3 to 3.6)	0.08 (0.04 to 0.13)	13.81
Anorexia	Diener, 2007[33]	50 to 200	2/32 [1/27]	6.3 [3.7]	1.7 (0.2 to 16.9)	0.03 (-0.09 to 0.14)	5.64
Anorexia	Adelman, 2008[39]	50	22/235 [6/92]	9.4 [6.1]	1.5 (0.6 to 3.4)	0.03 (-0.03 to 0.09)	10.85
Anorexia	Pooled	All doses	**220/1964 [70/1426]**	**11.2 [4.9]**	**2.1 (1.7 to 2.7)**	**0.05 (0.02 to 0.09)**	**100**
Anxiety	Adelman, 2008[39]	100	21/386 [4/151]	5.4 [2.7]	1.9 (0.8 to 4.6)	0.03 (-0.01 to 0.06)	31.58
Anxiety	Storey, 2001[17]	200	2/19 [0/21]	10.5 [0.0]	8.7 (0.5 to 144.3)	0.11 (-0.05 to 0.26)	1.48
Anxiety	Adelman, 2008[39]	200	30/514 [5/202]	5.8 [2.7]	2.1 (1.0 to 4.4)	0.03 (0.00 to 0.06)	42.19
Anxiety	Adelman, 2008[39]	50	9/235 [2/92]	3.8 [2.7]	1.7 (0.4 to 6.3)	0.02 (-0.02 to 0.06)	24.75
Anxiety	Pooled	All doses	62/1154 [12/466]	5.4 [2.6]	2.0 (1.2 to 3.4)	0.03 (0.01 to 0.05)	100
Paresthesia	Mei, 2004[23]	100	8/58 [1/57]	13.8 [1.8]	5.2 (1.3 to 20.3)	0.12 (0.03 to 0.22)	9.05
Paresthesia	Mei, 2006[27]	100	18/30 [2/20]	60.0 [10.0]	7.7 (2.5 to 24.2)	0.50 (0.28 to 0.72)	6.09

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Paresthesia	Silberstein, 2007[30]	100	48/165 [12/163]	28.8 [7.5]	4.3 (2.4 to 7.5)	0.22 (0.14 to 0.30)	9.35
Paresthesia	Adelman, 2008[39]	100	195/386 [9/151]	50.5 [5.8]	6.6 (4.5 to 9.8)	0.45 (0.38 to 0.51)	9.67
Paresthesia	Lipton, 2011[41]	100	57/188 [13/197]	30.3 [6.6]	4.9 (2.9 to 8.2)	0.24 (0.16 to 0.31)	9.46
Paresthesia	Diener, 2007[37]	100	77/255 [55/259]	30.2 [21.2]	1.6 (1.1 to 2.4)	0.09 (0.01 to 0.17)	9.45
Paresthesia	Edwards, 2003[18]	200	22/34 [8/36]	64.7 [22.2]	5.5 (2.2 to 14.2)	0.43 (0.21 to 0.64)	6.28
Paresthesia	Silberstein, 2006[28]	200	63/140 [4/73]	45.0 [5.5]	6.2 (3.4 to 11.4)	0.40 (0.30 to 0.49)	8.99
Paresthesia	Adelman, 2008[39]	200	254/514 [12/202]	49.4 [5.8]	6.4 (4.6 to 9.0)	0.44 (0.38 to 0.49)	9.79
Paresthesia	Diener, 2007[33]	50 to 200	17/32 [2/27]	53.1 [7.4]	7.8 (2.6 to 23.2)	0.46 (0.26 to 0.66)	6.55
Paresthesia	Silvestrini, 2003[19]	50	2/14 [1/14]	14.3 [7.1]	2.1 (0.2 to 21.6)	0.07 (-0.16 to 0.30)	5.9
Paresthesia	Adelman, 2008[39]	50	83/235 [5/92]	35.3 [5.8]	4.5 (2.6 to 7.8)	0.30 (0.22 to 0.38)	9.42
Paresthesia	Pooled	All doses	**844/2051 [124/1291]**	**41.1 [9.6]**	**4.6 (4.0 to 5.5)**	**0.30 (0.22 to 0.39)**	**100**
Back pain	Adelman, 2008[39]	100	15/386 [8/151]	3.9 [5.2]	0.7 (0.3 to 1.8)	-0.01 (-0.05 to 0.03)	26.2
Back pain	Lipton, 2011[41]	100	10/188 [10/197]	5.3 [5.1]	1.1 (0.4 to 2.6)	0.00 (-0.04 to 0.05)	21.72
Back pain	Adelman, 2008[39]	200	22/514 [10/202]	4.3 [5.2]	0.9 (0.4 to 1.9)	-0.01 (-0.04 to 0.03)	35.34
Back pain	Adelman, 2008[39]	50	6/235 [5/92]	2.6 [5.2]	0.4 (0.1 to 1.6)	-0.03 (-0.08 to 0.02)	16.75
Back pain	Pooled	All doses	53/1323 [33/642]	4.0 [5.1]	0.8 (0.5 to 1.3)	-0.01 (-0.03 to 0.01)	100
Difficulty with concentration	Mei, 2006[27]	100	4/30 [2/20]	13.3 [10.0]	1.4 (0.2 to 7.6)	0.03 (-0.15 to 0.21)	2.14
Difficulty with concentration	Silberstein, 2007[30]	100	16/165 [4/163]	9.4 [2.5]	3.5 (1.4 to 8.7)	0.07 (0.02 to 0.12)	14.31

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Difficulty with concentration	Adelman, 2008[39]	100	23/386 [3/151]	6.0 [2.3]	2.4 (1.0 to 5.7)	0.04 (0.01 to 0.07)	20.42
Disturbance in attention	Diener, 2007[37]	100	11/255 [12/259]	4.3 [4.6]	0.9 (0.4 to 2.1)	0.00 (-0.04 to 0.03)	19.24
Difficulty with concentration	Adelman, 2008[39]	200	51/514 [5/202]	9.9 [2.3]	2.8 (1.5 to 5.1)	0.07 (0.04 to 0.11)	20.02
Disturbance in attention	Diener, 2007[33]	50 to 200	2/32 [1/27]	6.3 [3.7]	1.7 (0.2 to 16.9)	0.03 (-0.09 to 0.14)	5.05
Difficulty with concentration	Adelman, 2008[39]	50	7/235 [2/92]	3.0 [2.3]	1.4 (0.3 to 5.9)	0.01 (-0.03 to 0.05)	18.83
Difficulty with concentration	Pooled	All doses	**114/1617 [29/914]**	**7.0 [3.2]**	**2.1 (1.5 to 3.0)**	**0.04 (0.01 to 0.06)**	**100**
Depression	Adelman, 2008[39]	100	15/386 [5/151]	3.9 [3.6]	1.2 (0.4 to 3.2)	0.01 (-0.03 to 0.04)	27.66
Depression	Diener, 2007[37]	100	13/255 [13/259]	5.1 [5.0]	1.0 (0.5 to 2.2)	0.00 (-0.04 to 0.04)	22.85
Depression	Adelman, 2008[39]	200	30/514 [7/202]	5.8 [3.6]	1.6 (0.8 to 3.4)	0.02 (-0.01 to 0.06)	31.16
Depression	Adelman, 2008[39]	50	7/235 [3/92]	3.0 [3.6]	0.9 (0.2 to 3.7)	0.00 (-0.05 to 0.04)	18.33
Depression	Pooled	All doses	65/1390 [29/704]	4.7 [4.1]	1.2 (0.8 to 1.9)	0.01 (-0.01 to 0.03)	100
Diarrhea	Adelman, 2008[39]	100	43/386 [6/151]	11.1 [4.3]	2.4 (1.2 to 4.6)	0.07 (0.03 to 0.12)	23.41
Diarrhea	Lipton, 2011[41]	100	11/188 [6/197]	5.9 [3.0]	1.9 (0.7 to 5.1)	0.03 (-0.01 to 0.07)	26.38
Diarrhea	Edwards, 2003[18]	200	7/34 [2/36]	20.6 [5.6]	3.8 (0.9 to 15.1)	0.15 (-0.01 to 0.31)	2.17
Diarrhea	Adelman, 2008[39]	200	54/514 [7/202]	10.5 [3.7]	2.5 (1.4 to 4.4)	0.07 (0.03 to 0.11)	32.07
Diarrhea	Adelman, 2008[39]	50	20/235 [4/92]	8.5 [4.5]	1.8 (0.7 to 4.6)	0.04 (-0.01 to 0.10)	15.97
Diarrhea	Pooled	All doses	**135/1357 [26/678]**	**9.9 [3.8]**	**2.3 (1.6 to 3.3)**	**0.06 (0.03 to 0.08)**	**100**
Dizziness	Mei, 2006[27]	100	0/30 [3/20]	0.0 [15.0]	0.1 (0.0 to 0.8)	-0.15 (-0.32 to 0.02)	1.29

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Dizziness	Silberstein, 2007[30]	100	6/165 [12/163]	3.8 [7.5]	0.5 (0.2 to 1.3)	-0.04 (-0.09 to 0.01)	11.55
Dizziness	Adelman, 2008[39]	100	33/386 [15/151]	8.5 [9.9]	0.8 (0.4 to 1.6)	-0.01 (-0.07 to 0.04)	9.62
Dizziness	Lipton, 2011[41]	100	20/188 [14/197]	10.6 [7.1]	1.5 (0.8 to 3.1)	0.04 (-0.02 to 0.09)	9.19
Dizziness	Diener, 2007[37]	100	1/255 [1/259]	0.4 [0.4]	1.0 (0.1 to 16.3)	0.00 (-0.01 to 0.01)	43.54
Dizziness	Silberstein, 2007[30]	200	22/140 [8/73]	15.7 [11.0]	1.5 (0.7 to 3.3)	0.05 (-0.05 to 0.14)	3.82
Dizziness	Adelman, 2008[39]	200	62/514 [20/202]	12.1 [9.9]	1.2 (0.7 to 2.1)	0.02 (-0.03 to 0.07)	11.31
Dizziness	Diener, 2007[33]	50 to 200	2/32 [0/27]	6.3 [0.0]	6.5 (0.4 to 108.0)	0.06 (-0.04 to 0.17)	3.22
Dizziness	Adelman, 2008[39]	50	19/235 [9/92]	8.1 [9.9]	0.8 (0.3 to 1.9)	-0.02 (-0.09 to 0.05)	6.46
Dizziness	Pooled	All doses	165/1945 [82/1184]	8.5 [6.9]	1.0 (0.8 to 1.4)	0.00 (-0.02 to 0.02)	100
Dry mouth	Silberstein, 2007[30]	100	16/165 [5/163]	9.4 [3.1]	3.0 (1.2 to 7.3)	0.07 (0.01 to 0.12)	12.16
Dry mouth	Adelman, 2008[39]	100	12/386 [4/151]	3.1 [2.5]	1.2 (0.4 to 3.6)	0.01 (-0.03 to 0.04)	23.85
Dry mouth	Lipton, 2011[41]	100	12/188 [5/197]	6.4 [2.5]	2.5 (0.9 to 6.6)	0.04 (0.00 to 0.08)	16.97
Dry mouth	Adelman, 2008[39]	200	26/514 [5/202]	5.1 [2.5]	1.9 (0.8 to 4.1)	0.03 (0.00 to 0.05)	25.63
Dry mouth	Adelman, 2008[39]	50	4/235 [2/92]	1.7 [2.5]	0.8 (0.1 to 4.6)	-0.01 (-0.04 to 0.03)	21.39
Dry mouth	Pooled	All doses	**70/1488 [21/805]**	**4.7 [2.6]**	**2.0 (1.3 to 3.1)**	**0.02 (0.00 to 0.04)**	**100**
Fatigue/asthenia	Mei, 2004[23]	100	4/58 [0/57]	6.9 [0.0]			
Fatigue	Mei, 2006[27]	100	8/30 [1/20]	26.7 [5.0]	4.2 (1.0 to 18.1)	0.22 (0.03 to 0.40)	1.24
Fatigue	Silberstein, 2007[30]	100	20/165 [16/163]	11.9 [9.9]	1.3 (0.6 to 2.5)	0.02 (-0.05 to 0.09)	9.28

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Fatigue	Adelman, 2008[39]	100	58/386 [17/151]	15.0 [11.2]	1.4 (0.8 to 2.4)	0.04 (-0.02 to 0.10)	11.12
Fatigue	Silberstein, 2009[40]	100	19/165 [16/163]	11.5 [9.8]	1.2 (0.6 to 2.4)	0.02 (-0.05 to 0.08)	9.51
Fatigue	Lipton, 2011[41]	100	26/188 [16/197]	13.8 [8.1]	1.8 (0.9 to 3.4)	0.06 (-0.01 to 0.12)	10.89
Fatigue	Diener, 2007[37]	100	18/255 [10/259]	7.1 [3.9]	1.9 (0.9 to 4.0)	0.03 (-0.01 to 0.07)	27.54
Fatigue	Silberstein, 2006[28]	200	22/140 [6/73]	15.7 [8.2]	1.9 (0.8 to 4.4)	0.08 (-0.01 to 0.16)	5.57
Fatigue	Adelman, 2008[39]	200	98/514 [23/202]	19.1 [11.2]	1.7 (1.1 to 2.7)	0.08 (0.02 to 0.13)	13.8
Fatigue	Diener, 2007[33]	50 to 200	2/32 [0/27]	6.3 [0.0]	6.5 (0.4 to 108.0)	0.06 (-0.04 to 0.17)	4.01
Fatigue	Adelman, 2008[39]	50	33/235 [10/92]	14.0 [11.2]	1.3 (0.6 to 2.7)	0.03 (-0.05 to 0.11)	7.04
Fatigue	Pooled	All doses	**308/2168 [115/1404]**	**14.2 [8.2]**	**1.6 (1.3 to 2.0)**	**0.05 (0.03 to 0.07)**	**100**
Hypoesthesia	Silberstein, 2007[30]	100	16/165 [0/163]	9.4 [0.0]	8.0 (2.9 to 21.9)	0.10 (0.05 to 0.14)	12.65
Hypoesthesia	Adelman, 2008[39]	100	28/386 [3/151]	7.3 [1.8]	2.6 (1.2 to 5.9)	0.05 (0.02 to 0.09)	20.32
Hypoesthesia	Silberstein, 2009[40]	100	15/165 [0/163]	9.1 [0.0]	8.0 (2.8 to 22.5)	0.09 (0.05 to 0.14)	13.22
Hypoesthesia	Lipton, 2011[41]	100	12/188 [5/197]	6.4 [2.5]	2.5 (0.9 to 6.6)	0.04 (0.00 to 0.08)	15.21
Hypoesthesia	Adelman, 2008[39]	200	40/514 [4/202]	7.8 [1.8]	2.7 (1.4 to 5.4)	0.06 (0.03 to 0.09)	24.07
Hypoesthesia	Adelman, 2008[39]	50	14/235 [2/92]	6.0 [1.8]	2.2 (0.7 to 6.9)	0.04 (-0.01 to 0.08)	14.54
Hypoesthesia	Pooled	All doses	**125/1653 [13/968]**	**7.5 [1.3]**	**3.5 (2.4 to 5.0)**	**0.06 (0.04 to 0.08)**	**100**
Injury	Silberstein, 2007[30]	100	8/165 [2/163]	5.0 [1.2]	3.4 (1.0 to 11.9)	0.04 (0.00 to 0.07)	18.28
Injury	Adelman, 2008[39]	100	25/386 [10/151]	6.5 [6.7]	1.0 (0.5 to 2.1)	0.00 (-0.05 to 0.05)	16.12

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Injury	Silberstein, 2009[40]	100	8/165 [2/163]	4.8 [1.2]	3.4 (1.0 to 11.9)	0.04 (0.00 to 0.07)	18.28
Injury	Lipton, 2011[41]	100	3/188 [17/197]	1.6 [8.6]	0.2 (0.1 to 0.6)	-0.07 (-0.11 to -0.03)	16.89
Injury	Adelman, 2008[39]	200	32/514 [14/202]	6.2 [6.7]	0.9 (0.5 to 1.7)	-0.01 (-0.05 to 0.03)	17.41
Injury	Adelman, 2008[39]	50	20/235 [6/92]	8.5 [6.7]	1.3 (0.5 to 3.2)	0.02 (-0.04 to 0.08)	13.02
Injury	Pooled	All doses	96/1653 [51/968]	5.8 [5.3]	1.0 (0.7 to 1.4)	0.00 (-0.03 to 0.04)	100
Insomnia	Mei, 2006[27]	100	1/30 [2/20]	3.3 [10.0]	0.3 (0.0 to 3.3)	-0.07 (-0.21 to 0.08)	2.6
Insomnia	Adelman, 2008[39]	100	27/386 [7/151]	7.0 [4.7]	1.5 (0.7 to 3.2)	0.02 (-0.02 to 0.07)	31.38
Insomnia	Edwards, 2003[18]	200	4/34 [3/36]	11.8 [8.3]	1.5 (0.3 to 6.9)	0.03 (-0.11 to 0.18)	2.8
Insomnia	Adelman, 2008[39]	200	32/514 [10/202]	6.2 [4.7]	1.3 (0.6 to 2.5)	0.01 (-0.02 to 0.05)	41.77
Insomnia	Adelman, 2008[39]	50	13/235 [4/92]	5.5 [4.7]	1.3 (0.4 to 3.8)	0.01 (-0.04 to 0.06)	21.46
Insomnia	Pooled	All doses	77/1199 [26/501]	6.4 [5.2]	1.3 (0.8 to 2.0)	0.01 (-0.01 to 0.04)	100
Cognitive symptom	Mei, 2004[23]	100	3/58 [0/57]	5.2 [0.0]			
Memory impairment	Mei, 2006[27]	100	5/30 [2/20]	16.7 [10.0]	1.7 (0.3 to 8.6)	0.07 (-0.12 to 0.25)	1.68
Difficulty with memory	Silberstein, 2007[30]	100	11/165 [10/163]	6.9 [6.2]	1.1 (0.5 to 2.6)	0.01 (-0.05 to 0.06)	14.14
Difficulty with memory	Adelman, 2008[39]	100	26/386 [3/151]	6.7 [2.3]	2.5 (1.1 to 5.8)	0.05 (0.01 to 0.08)	23.08
Memory impairment	Edwards, 2003[18]	200	6/34 [2/36]	17.6 [5.6]	3.2 (0.8 to 14.0)	0.12 (-0.03 to 0.27)	2.61
Difficulty with memory	Silberstein, 2006[28]	200	15/140 [1/73]	10.7 [1.4]	3.8 (1.3 to 11.1)	0.09 (0.04 to 0.15)	12.61
Difficulty with memory	Adelman, 2008[39]	200	57/514 [5/202]	11.1 [2.3]	3.0 (1.7 to 5.3)	0.09 (0.05 to 0.12)	22.44

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Memory impairment	Diener, 2007[33]	50 to 200	1/32 [1/27]	3.1 [3.7]	0.8 (0.1 to 13.9)	-0.01 (-0.10 to 0.09)	6
Difficulty with memory	Adelman, 2008[39]	50	17/235 [2/92]	7.2 [2.3]	2.5 (0.9 to 7.0)	0.05 (0.01 to 0.10)	17.43
Cognitive symptoms	Pooled	All doses	**141/1594 [26/821]**	**8.9 [3.2]**	**2.4 (1.7 to 3.4)**	**0.06 (0.03 to 0.08)**	**100**
Nausea	Silberstein, 2007[30]	100	15/165 [13/163]	8.8 [8.1]	1.2 (0.5 to 2.5)	0.01 (-0.05 to 0.07)	11.85
Nausea	Adelman, 2008[39]	100	51/386 [13/151]	13.2 [8.3]	1.6 (0.9 to 2.8)	0.05 (-0.01 to 0.10)	13.29
Nausea	Lipton, 2011[41]	100	19/188 [17/197]	10.1 [8.6]	1.2 (0.6 to 2.4)	0.02 (-0.04 to 0.07)	12.51
Nausea	Diener, 2007[37]	100	11/255 [10/259]	4.3 [3.9]	1.1 (0.5 to 2.7)	0.01 (-0.03 to 0.04)	23.81
Nausea	Silberstein, 2006[28]	200	20/140 [3/73]	14.3 [4.1]	2.9 (1.2 to 7.1)	0.10 (0.03 to 0.18)	8.71
Nausea	Adelman, 2008[39]	200	73/514 [17/202]	14.2 [8.3]	1.7 (1.0 to 2.8)	0.06 (0.01 to 0.11)	15.98
Nausea	Diener, 2007[33]	50 to 200	3/32 [0/27]	9.4 [0.0]	6.8 (0.7 to 68.1)	0.09 (-0.02 to 0.21)	3.98
Nausea	Adelman, 2008[39]	50	21/235 [8/92]	8.9 [8.3]	1.0 (0.4 to 2.4)	0.00 (-0.07 to 0.07)	9.87
Nausea	Pooled	All doses	**213/1915 [80/1164]**	**11.1 [6.9]**	**1.5 (1.1 to 1.9)**	**0.03 (0.01 to 0.06)**	**100**
Sinusitis	Silberstein, 2007[30]	100	7/165 [8/163]	4.4 [5.0]	0.9 (0.3 to 2.4)	-0.01 (-0.05 to 0.04)	22.94
Sinusitis	Adelman, 2008[39]	100	25/386 [10/151]	6.5 [6.3]	1.0 (0.5 to 2.1)	0.00 (-0.05 to 0.05)	21.76
Sinusitis	Lipton, 2011[41]	100	16/188 [15/197]	8.5 [7.6]	1.1 (0.5 to 2.4)	0.01 (-0.05 to 0.06)	15.84
Sinusitis	Adelman, 2008[39]	200	41/514 [13/202]	8.0 [6.3]	1.2 (0.7 to 2.3)	0.02 (-0.03 to 0.06)	27.7
Sinusitis	Adelman, 2008[39]	50	23/235 [6/92]	9.8 [6.3]	1.5 (0.6 to 3.5)	0.03 (-0.03 to 0.10)	11.76
Sinusitis	Pooled	All doses	112/1488 [51/805]	7.5 [6.4]	1.2 (0.8 to 1.6)	0.01 (-0.01 to 0.03)	100

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Somnolence	Mei, 2004[23]	100	2/58 [9/57]	3.4 [15.8]	0.2 (0.1 to 0.8)	-0.12 (-0.23 to -0.02)	3.13
Somnolence	Mei, 2006[27]	100	2/30 [0/20]	6.7 [0.0]	5.5 (0.3 to 95.6)	0.07 (-0.05 to 0.18)	2.63
Somnolence	Silberstein, 2007[30]	100	9/165 [7/163]	5.6 [4.3]	1.3 (0.5 to 3.5)	0.01 (-0.04 to 0.06)	12.91
Somnolence	Adelman, 2008[39]	100	26/386 [8/151]	6.7 [5.4]	1.3 (0.6 to 2.8)	0.01 (-0.03 to 0.06)	14.23
Somnolence	Silberstein, 2009[40]	100	9/165 [7/163]	5.5 [4.3]	1.3 (0.5 to 3.5)	0.01 (-0.04 to 0.06)	12.91
Somnolence	Lipton, 2011[41]	100	9/188 [3/197]	4.8 [1.5]	2.9 (0.9 to 9.3)	0.03 (0.00 to 0.07)	19.21
Somnolence	Silberstein, 2006[28]	200	16/140 [4/73]	11.4 [5.5]	2.0 (0.8 to 5.3)	0.06 (-0.02 to 0.13)	5.99
Somnolence	Adelman, 2008[39]	200	51/514 [11/202]	9.9 [5.4]	1.8 (1.0 to 3.1)	0.05 (0.00 to 0.09)	15.77
Somnolence	Diener, 2007[33]	50 to 200	1/32 [1/27]	3.1 [3.7]	0.8 (0.1 to 13.9)	-0.01 (-0.10 to 0.09)	3.95
Somnolence	Adelman, 2008[39]	50	18/235 [5/92]	7.7 [5.4]	1.4 (0.5 to 3.6)	0.02 (-0.04 to 0.08)	9.27
Somnolence	Pooled	All doses	143/1913 [55/1145]	7.5 [4.8]	1.4 (1.1 to 2.0)	0.02 (0.00 to 0.04)	100
Alteration of taste	Mei, 2006[27]	100	10/30 [0/20]	33.3 [0.0]	7.7 (1.9 to 31.2)	0.33 (0.15 to 0.51)	46.31
Alteration of taste	Edwards, 2003[18]	200	11/34 [1/36]	32.4 [2.8]	7.8 (2.3 to 26.8)	0.30 (0.13 to 0.46)	53.69
Alteration of taste	Pooled	All doses	**21/64 [1/56]**	**32.8 [1.8]**	**7.8 (3.1 to 19.6)**	**0.31 (0.19 to 0.44)**	**100**
Taste perversion	Silberstein, 2007[30]	100	16/165 [4/163]	9.4 [2.5]	3.5 (1.4 to 8.7)	0.07 (0.02 to 0.12)	13.62
Taste perversion	Adelman, 2008[39]	100	30/386 [2/151]	7.8 [1.1]	3.2 (1.4 to 7.0)	0.07 (0.03 to 0.10)	21.18
Taste perversion	Silberstein, 2009[40]	100	15/165 [4/163]	9.1 [2.5]	3.4 (1.3 to 8.5)	0.07 (0.02 to 0.12)	13.99
Taste perversion	Lipton, 2011[41]	100	17/188 [3/197]	9.0 [1.5]	4.6 (1.9 to 11.3)	0.08 (0.03 to 0.12)	15.91

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Taste perversion	Adelman, 2008[39]	200	63/514 [2/202]	12.3 [1.1]	3.9 (2.2 to 6.9)	0.11 (0.08 to 0.14)	21.56
Taste perversion	Adelman, 2008[39]	50	36/235 [1/92]	15.3 [1.1]	4.1 (1.9 to 8.8)	0.14 (0.09 to 0.19)	13.73
Taste perversion	Pooled	All doses	**177/1653 [16/968]**	**10.7 [1.7]**	**3.8 (2.8 to 5.2)**	**0.09 (0.06 to 0.11)**	**100**
Upper respiratory tract infection	Silberstein, 2007[30]	100	23/165 [20/163]	13.8 [12.4]	1.2 (0.6 to 2.2)	0.02 (-0.06 to 0.09)	12.26
Upper respiratory tract infection	Adelman, 2008[39]	100	54/386 [18/151]	14.0 [12.1]	1.2 (0.7 to 2.1)	0.02 (-0.04 to 0.08)	16.9
Upper respiratory tract infection	Lipton, 2011[41]	100	16/188 [12/197]	8.5 [6.1]	1.4 (0.7 to 3.1)	0.02 (-0.03 to 0.08)	24.15
Upper respiratory tract infection	Silberstein, 2006[28]	200	18/140 [7/73]	12.9 [9.6]	1.4 (0.6 to 3.3)	0.03 (-0.06 to 0.12)	8.56
Upper respiratory tract infection	Adelman, 2008[39]	200	62/514 [24/202]	12.1 [12.1]	1.0 (0.6 to 1.7)	0.00 (-0.05 to 0.05)	23.33
Upper respiratory tract infection	Adelman, 2008[39]	50	31/235 [6/92]	13.2 [7.0]	1.9 (0.9 to 4.1)	0.07 (0.00 to 0.13)	14.8
Upper respiratory tract infection	Pooled	All doses	204/1628 [88/878]	12.5 [10.1]	1.2 (1.0 to 1.6)	0.02 (0.00 to 0.05)	100
Abnormal vision	Adelman, 2008[39]	100	14/386 [4/151]	3.6 [2.5]	1.4 (0.5 to 3.9)	0.01 (-0.02 to 0.04)	35.05
Abnormal vision	Storey, 2001[17]	200	3/19 [0/21]	15.8 [0.0]	9.2 (0.9 to 94.2)	0.16 (-0.02 to 0.34)	2.3
Abnormal vision	Adelman, 2008[39]	200	38/514 [5/202]	7.4 [2.5]	2.4 (1.2 to 4.7)	0.05 (0.02 to 0.08)	35.45
Abnormal vision	Adelman, 2008[39]	50	11/235 [2/92]	4.7 [2.5]	1.9 (0.6 to 6.6)	0.03 (-0.02 to 0.07)	27.2
Abnormal vision	Pooled	All doses	**66/1154 [11/466]**	**5.7 [2.4]**	**2.1 (1.3 to 3.6)**	**0.03 (0.00 to 0.06)**	**100**
Weight loss	Mei, 2004[23]	100	8/58 [0/57]	13.8 [0.0]			
Weight loss	Mei, 2006[27]	100	7/30 [0/20]	23.3 [0.0]	6.7 (1.3 to 33.6)	0.23 (0.07 to 0.40)	4.33
Weight loss	Adelman, 2008[39]	100	35/386 [2/151]	9.1 [1.4]	3.3 (1.6 to 7.0)	0.08 (0.04 to 0.11)	21.13

Appendix Table D132. Adverse effects with topiramate in adults with migraine (pooled results from individual randomized controlled clinical trials) (continued)

Outcome	Reference	Dose, mg/day	Events/ randomized with drug [placebo]	Rate % with drug [placebo]	Peto odds ratio (95% CI)	Absolute risk difference (95% CI)	Weight Random effects Inverse variance
Weight loss	Diener, 2007[37]	100	23/255 [18/259]	9.0 [6.9]	1.3 (0.7 to 2.5)	0.02 (-0.03 to 0.07)	18.27
Weight loss	Storey, 2001[17]	200	10/19 [6/21]	52.6 [28.6]	2.7 (0.8 to 9.3)	0.24 (-0.06 to 0.54)	1.51
Weight loss	Silberstein, 2006[28]	200	19/140 [1/73]	13.6 [1.4]	4.2 (1.6 to 11.0)	0.12 (0.06 to 0.19)	14.91
Weight loss	Adelman, 2008[39]	200	58/514 [3/202]	11.3 [1.4]	3.5 (2.0 to 6.3)	0.10 (0.07 to 0.13)	21.54
Weight loss	Adelman, 2008[39]	5	13/235 [3/92]	5.5 [2.9]	1.6 (0.5 to 5.0)	0.02 (-0.02 to 0.07)	18.32
Weight loss	Pooled	All doses	**173/1637 [32/875]**	**10.6 [3.7]**	**2.6 (1.9 to 3.6)**	**0.08 (0.04 to 0.12)**	**100**

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D133. Significant dose response adverse effects with topiramate in adults

Adverse effect	Reference Risk of bias	Active vs. control daily dose	Events/randomized (rate of outcome in active group) Events/randomized (rate of outcome in control group)	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abnormal vision	Adelman, 2008[39] Risk of bias Low	200 vs. 50	6/514 (1.2) 12/235 (5.1)	0.2 (0.1 to 0.6)	-0.04 (-0.07 to -0.01)
Abnormal vision	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**38/514 (7.4) 14/386 (3.6)**	**2.0 (1.1 to 3.7)**	**0.04 (0.01 to 0.07)**
Anorexia	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**56/386 (14.5) 22/235 (9.4)**	**1.5 (1.0 to 2.5)**	**0.05 (0.00 to 0.10)**
Anorexia leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**14/514 (2.7) 2/235 (0.9)**	**3.2 (0.7 to 14.0)**	**0.02 (0.00 to 0.04)**
Any adverse event	Adelman, 2008[39] Risk of bias Low	200 vs. 100	187/514 (36.4) 227/386 (58.8)	0.6 (0.5 to 0.7)	-0.22 (-0.29 to -0.16)
Arthralgia	Adelman, 2008[39] Risk of bias Low	100 vs. 50	11/386 (2.8) 17/235 (7.2)	0.4 (0.2 to 0.8)	-0.04 (-0.08 to -0.01)
Arthralgia	Adelman, 2008[39] Risk of bias Low	200 vs. 50	7/514 (1.4) 17/235 (7.2)	0.2 (0.1 to 0.4)	-0.06 (-0.09 to -0.02)
Arthralgia	Adelman, 2008[39] Risk of bias Low	200 vs. 50	4/514 (0.8) 8/235 (3.4)	0.2 (0.1 to 0.8)	-0.03 (-0.05 to 0.00)
Depression leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**14/514 (2.7) 1/235 (0.4)**	**6.4 (0.8 to 48.4)**	**0.02 (0.01 to 0.04)**
Depression leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**14/514 (2.7) 3/386 (0.8)**	**3.5 (1.0 to 12.1)**	**0.02 (0.00 to 0.04)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**8/386 (2.1) 1/235 (0.4)**	**4.9 (0.6 to 38.7)**	**0.02 (0.00 to 0.03)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**24/514 (4.7) 1/235 (0.4)**	**11.0 (1.5 to 80.6)**	**0.04 (0.02 to 0.06)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**24/514 (4.7) 8/386 (2.1)**	**2.3 (1.0 to 5.0)**	**0.03 (0.00 to 0.05)**
Difficulty with concentration/attention	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**51/514 (9.9) 7/235 (3.0)**	**3.3 (1.5 to 7.2)**	**0.07 (0.04 to 0.10)**
Difficulty with concentration/attention	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**51/514 (9.9) 23/386 (6.0)**	**1.7 (1.0 to 2.7)**	**0.04 (0.00 to 0.07)**
Difficulty with memory	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**57/514 (11.1) 26/386 (6.7)**	**1.6 (1.1 to 2.6)**	**0.04 (0.01 to 0.08)**
Dry mouth	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**26/514 (5.1) 4/235 (1.7)**	**3.0 (1.0 to 8.4)**	**0.03 (0.01 to 0.06)**
Hypoesthesia leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**12/514 (2.3) 1/235 (0.4)**	**5.5 (0.7 to 41.9)**	**0.02 (0.00 to 0.03)**

Appendix Table 133. Significant dose response adverse effects with topiramate in adults (continued)

Adverse effect	Reference Risk of bias	Active vs. control daily dose	Events/randomized (rate of outcome in active group) Events/randomized (rate of outcome in control group)	Relative risk (95% CI)	Absolute risk difference (95% CI)
Marked anorexia	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**6/514 (1.2) 0/235 (0.0)**	**6.0 (0.3 to 105.3)**	**0.01 (0.00 to 0.02)**
Marked fatigue	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**6/386 (1.6) 0/235 (0.0)**	**7.9 (0.4 to 140.1)**	**0.02 (0.00 to 0.03)**
Marked fatigue	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**15/514 (2.9) 0/235 (0.0)**	**14.2 (0.9 to 236.4)**	**0.03 (0.01 to 0.05)**
Marked paresthesia	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**20/514 (3.9) 3/235 (1.3)**	**3.0 (0.9 to 10.2)**	**0.03 (0.00 to 0.05)**
Markedly low serum bicarbonate levels (range >5mmol/L to <17mmo/L below baseline)	Adelman, 2008[39] Risk of bias Low	50 vs. 0	5/235 (2.0) 57/514 (11.0)	0.2 (0.1 to 0.5)	-0.09 (-0.12 to -0.06)
Markedly low serum bicarbonate levels (range >5mmol/L to <17mmo/L below baseline)	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**35/386 (9.0) 5/235 (2.0)**	**4.3 (1.7 to 10.7)**	**0.07 (0.04 to 0.10)**
Mild paresthesia	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**130/386 (33.7) 54/235 (23.0)**	**1.5 (1.1 to 1.9)**	**0.11 (0.04 to 0.18)**
Mild paresthesia	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**169/514 (32.9) 54/235 (23.0)**	**1.4 (1.1 to 1.9)**	**0.10 (0.03 to 0.17)**
Moderate anorexia	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**23/386 (6.0) 4/235 (1.7)**	**3.5 (1.2 to 10.0)**	**0.04 (0.01 to 0.07)**
Moderate anorexia	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**22/514 (4.3) 4/235 (1.7)**	**2.5 (0.9 to 7.2)**	**0.03 (0.00 to 0.05)**
Moderate nausea	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**36/514 (7.0) 7/235 (3.0)**	**2.4 (1.1 to 5.2)**	**0.04 (0.01 to 0.07)**
Mood problems	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**23/386 (6.0) 6/235 (2.6)**	**2.3 (1.0 to 5.6)**	**0.03 (0.00 to 0.07)**
Mood problems	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**28/514 (5.4) 6/235 (2.6)**	**2.1 (0.9 to 5.1)**	**0.03 (0.00 to 0.06)**
Nausea	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**16/386 (4.1) 2/235 (0.9)**	**4.9 (1.1 to 21.0)**	**0.03 (0.01 to 0.06)**
Nausea	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**51/235 (21.7) 21/386 (5.4)**	**4.0 (2.5 to 6.5)**	**0.16 (0.11 to 0.22)**
Nausea	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**73/235 (31.1) 21/514 (4.1)**	**7.6 (4.8 to 12.0)**	**0.27 (0.21 to 0.33)**
Nausea	Adelman, 2008[39] Risk of bias Low	200 vs. 100	8/514 (1.6) 16/386 (4.1)	0.4 (0.2 to 0.9)	-0.03 (-0.05 to 0.00)
Nausea	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**73/386 (18.9) 51/514 (9.9)**	**1.9 (1.4 to 2.7)**	**0.09 (0.04 to 0.14)**

Appendix Table 133. Significant dose response adverse effects with topiramate in adults (continued)

Adverse effect	Reference Risk of bias	Active vs. control daily dose	Events/randomized (rate of outcome in active group) Events/randomized (rate of outcome in control group)	Relative risk (95% CI)	Absolute risk difference (95% CI)
Nausea leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**29/514 (5.6) 9/386 (2.3)**	**2.4 (1.2 to 5.1)**	**0.03 (0.01 to 0.06)**
Paresthesia	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**34/386 (8.8) 11/235 (4.7)**	**1.9 (1.0 to 3.6)**	**0.04 (0.00 to 0.08)**
Paresthesia	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**195/386 (50.5) 83/235 (35.3)**	**1.4 (1.2 to 1.7)**	**0.15 (0.07 to 0.23)**
Paresthesia	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**254/514 (49.4) 83/235 (35.3)**	**1.4 (1.2 to 1.7)**	**0.14 (0.07 to 0.22)**
Paresthesia leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**100 vs. 50**	**31/386 (8.0) 8/235 (3.4)**	**2.4 (1.1 to 5.0)**	**0.05 (0.01 to 0.08)**
Paresthesia leading to withdrawal	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**37/514 (7.2) 8/235 (3.4)**	**2.1 (1.0 to 4.5)**	**0.04 (0.01 to 0.07)**
Pharyngitis	Adelman, 2008[39] Risk of bias Low	200 vs. 50	9/514 (1.8) 11/235 (4.7)	0.4 (0.2 to 0.9)	-0.03 (-0.06 to 0.00)
Pharyngitis	Adelman, 2008[39] Risk of bias Low	200 vs. 100	9/514 (1.8) 22/386 (5.7)	0.3 (0.1 to 0.7)	-0.04 (-0.07 to -0.01)
Pharyngitis	Adelman, 2008[39] Risk of bias Low	200 vs. 100	4/514 (0.8) 12/386 (3.1)	0.3 (0.1 to 0.8)	-0.02 (-0.04 to 0.00)
Taste perversion	Adelman, 2008[39] Risk of bias Low	100 vs. 50	30/386 (7.8) 36/235 (15.3)	0.5 (0.3 to 0.8)	-0.08 (-0.13 to -0.02)
Taste perversion	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**63/514 (12.3) 30/386 (7.8)**	**1.6 (1.0 to 2.4)**	**0.04 (0.01 to 0.08)**
Treatment discontinuation	Adelman, 2008[39] Risk of bias Low	100 vs. 50	146/386 (37.8) 108/235 (46.0)	0.8 (0.7 to 1.0)	-0.08 (-0.16 to 0.00)
Treatment discontinuation	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**149/514 (29.0) 41/235 (17.4)**	**1.7 (1.2 to 2.3)**	**0.12 (0.05 to 0.18)**
Treatment discontinuation	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 100**	**239/514 (46.5) 146/386 (37.8)**	**1.2 (1.0 to 1.4)**	**0.09 (0.02 to 0.15)**
Upper respiratory tract infection	Adelman, 2008[39] Risk of bias Low	200 vs. 100	32/514 (6.2) 42/386 (10.9)	0.6 (0.4 to 0.9)	-0.05 (-0.08 to -0.01)
Weight loss	**Adelman, 2008[39] Risk of bias Low**	**200 vs. 50**	**58/514 (11.3) 13/235 (5.5)**	**2.0 (1.1 to 3.6)**	**0.06 (0.02 to 0.10)**

Bold - significant increase in risk of adverse effects with increasing the dose of topiramate
CI – confidence interval

Appendix Table D134. Treatment discontinuation due to bothersome adverse effects with divalproex vs. placebo, results from randomized controlled clinical trials

Outcome	Daily dose	Reference Risk of bias	Events/ randomized with divalproex	Events/ randomized with placebo	Rate, % with divalproex [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Discontinuations due to intolerance	Mean average dose 1087 mg/d	Mathew, 1995[43] Risk of bias Moderate	9/70	2/37	12.9[5.4]	2.4 (0.5 to 10.4)	0.07 (-0.03 to 0.18)
Discontinuations due to intolerance	Mean average dose 871 mg/d	Freitag, 2002[44] Risk of bias Low	10/123	10/116	8.1[8.6]	0.9 (0.4 to 2.2)	0.00 (-0.08 to 0.07)
Discontinuations due to intolerance		Pooled	19/193	12/153	9.8[7.8]	1.2 (0.5 to 2.7)	0.02 (-0.05 to 0.10)
Discontinuations due to intolerance		Heterogeneity				p = 0.286/0.12	p = 0.224/0.323
Discontinuations due to ineffectiveness	Mean average dose 1087 mg/d	Mathew, 1995[43] Risk of bias Moderate	1/70	0/37	1.4[0.0]	1.6 (0.1 to 38.5)	0.01 (-0.04 to 0.06)
Abdominal pain	1000 mg	Klapper, 1997[45] Risk of bias Low	1/43	0/44	2.3[0.0]	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.09)
Alopecia	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Alopecia	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Asthenia	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Back pain	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Constipation	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Depression	1000 mg	Klapper, 1997[45] Risk of bias Low	3/43	0/44	7.0[0.0]	7.2 (0.4 to 134.6)	0.07 (-0.02 to 0.16)
Diarrhoea	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Emotional liability	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Gastrointestinal disorder	500 mg	Klapper, 1997[45] Risk of bias Low	0/45	0/15	0.0[2.3]	0.0 (0.0 to 0.0)	0.00 (-0.09 to 0.09)
Gastrointestinal disorder	1000 mg	Klapper, 1997[45] Risk of bias Low	0/43	0/14	0.0[2.3]	0.0 (0.0 to 0.0)	0.00 (-0.10 to 0.10)
Gastrointestinal disorder	1500 mg	Klapper, 1997[45] Risk of bias Low	0/44	0/15	0.0[2.3]	0.0 (0.0 to 0.0)	0.00 (-0.10 to 0.10)

Appendix Table 134. Treatment discontinuation due to bothersome adverse effects with divalproex vs. placebo, results from randomized controlled clinical trials (continued)

Outcome	Daily dose	Reference Risk of bias	Events/ randomized with divalproex	Events/ randomized with placebo	Rate, % with divalproex [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Nausea	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Nausea	1000 mg	Klapper, 1997[45] Risk of bias Low	1/43	0/44	2.3[0.0]	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.09)
Nausea	1500 mg	Klapper, 1997[45] Risk of bias Low	4/44	0/44	9.1[0.0]	9.0 (0.5 to 162.3)	0.09 (0.00 to 0.18)
Pharyngitis	1000 mg	Klapper, 1997[45] Risk of bias Low	1/43	0/44	2.3[0.0]	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.09)
Pneumonia	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Rash	500 mg	Klapper, 1997[45] Risk of bias Low	0/45	0/15	0.0[2.3]		0.00 (-0.09 to 0.09)
Rash	1000 mg	Klapper, 1997[45] Risk of bias Low	0/43	0/14	0.0[2.3]		0.00 (-0.10 to 0.10)
Rash	1500 mg	Klapper, 1997[45] Risk of bias Low	0/44	0/15	0.0[2.3]		0.00 (-0.10 to 0.10)
Somnolence	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Thinking abnormal	1500 mg	[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Vomiting	500 mg	Klapper, 1997[45] Risk of bias Low	1/45	0/44	2.2[0.0]	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Vomiting	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Weight gain	1500 mg	Klapper, 1997[45] Risk of bias Low	1/44	0/44	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)

CI –confidence interval

Appendix Table D135. Strength of evidence of treatment discontinuation due to bothersome adverse effects with divalproex vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials

Outcome	Daily dose	Reference	Sample	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Discontinuations due to intolerance	Mean average dose was 1087 mg/d	Mathew, 1995[43]	107	Moderate				
Discontinuations due to intolerance	Mean average dose of study: 871 mg/d	Freitag, 2002[44]	239	Low				
Discontinuations due to intolerance	Pooled		346	Moderate	Yes	Yes	No	Low

Appendix Table D136. Dose response in treatment discontinuation due to bothersome adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[45]

Adverse effect that lead to discontinuation	Daily doses of divalproex	Events/randomized with larger dose	Events/randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abdominal pain	1000 mg vs. 500 mg	1/43	0/45	3.1 (0.1 to 75.0)	0.02 (-0.04 to 0.08)
Abdominal pain	1500 mg vs. 1000 mg	0/44	1/43	0.3 (0.0 to 7.8)	-0.02 (-0.09 to 0.04)
Alopecia	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Alopecia	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Asthenia	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Asthenia	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Back pain	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Back pain	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Constipation	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Constipation	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Depression	1000 mg vs. 500 mg	3/43	0/45	7.3 (0.4 to 137.6)	0.07 (-0.02 to 0.16)
Depression	1500 mg vs. 1000 mg	0/44	3/43	0.1 (0.0 to 2.6)	-0.07 (-0.16 to 0.02)
Diarrhea	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Diarrhea	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Emotional liability	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Emotional liability	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Nausea	1000 mg vs. 500 mg	1/43	1/45	1.0 (0.1 to 16.2)	0.00 (-0.06 to 0.06)
Nausea	1500 mg vs. 500 mg	4/44	1/45	4.1 (0.5 to 35.2)	0.07 (-0.03 to 0.16)

Appendix Table D136. Dose response in treatment discontinuation due to bothersome adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[44] (continued)

Adverse effect that lead to discontinuation	Daily doses of divalproex	Events/randomized with larger dose	Events/randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI)
Nausea	1500 mg vs. 1000 mg	4/44	1/43	3.9 (0.5 to 33.6)	0.07 (-0.03 to 0.16)
Pharyngitis	1000 mg vs. 500 mg	1/43	0/45	3.1 (0.1 to 75.0)	0.02 (-0.04 to 0.08)
Pharyngitis	1500 mg vs. 1000 mg	0/44	1/43	0.3 (0.0 to 7.8)	-0.02 (-0.09 to 0.04)
Pneumonia	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Pneumonia	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Somnolence	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Somnolence	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Thinking abnormal	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Thinking abnormal	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Vomiting	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Vomiting	1500 mg vs. 500 mg	1/44	1/45	1.0 (0.1 to 15.8)	0.00 (-0.06 to 0.06)
Vomiting	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Weight gain	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Weight gain	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)

CI – confidence interval

Appendix Table D137. Dose response in adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[45]

Adverse effect	Daily doses of divalproex	Events/ randomized with larger dose	Events/ randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI	Attributable events per 1000 treated (95% CI)
Asthenia	1000 mg vs. 500 mg	4/43	4/45	1.0 (0.3 to 3.9)	0.00 (-0.12 to 0.12)	NS
Asthenia	1500 mg vs. 500 mg	10/44	4/45	2.6 (0.9 to 7.5)	0.14 (-0.01 to 0.29)	NS
Asthenia	1500 mg vs. 1000 mg	10/44	4/43	2.4 (0.8 to 7.2)	0.13 (-0.02 to 0.29)	NS
Back pain	1000 mg vs. 500 mg	2/43	3/45	0.7 (0.1 to 4.0)	-0.02 (-0.12 to 0.08)	NS
Back pain	1500 mg vs. 500 mg	6/44	3/45	2.0 (0.5 to 7.7)	0.07 (-0.06 to 0.19)	NS
Back pain	1500 mg vs. 1000 mg	6/44	2/43	2.9 (0.6 to 13.7)	0.09 (-0.03 to 0.21)	NS
Diarrhea	1000 mg vs. 500 mg	2/43	3/45	0.7 (0.1 to 4.0)	-0.02 (-0.12 to 0.08)	NS
Diarrhea	1500 mg vs. 500 mg	8/44	3/45	2.7 (0.8 to 9.6)	0.12 (-0.02 to 0.25)	NS
Diarrhea	**1500 mg vs. 1000 mg**	**8/44**	**2/43**	**3.9 (0.9 to 17.4)**	**0.14 (0.01 to 0.27)**	**135 (5 to 265)**
Dizziness	1000 mg vs. 500 mg	3/43	3/45	1.0 (0.2 to 4.9)	0.00 (-0.10 to 0.11)	NS
Dizziness	1500 mg vs. 500 mg	9/44	3/45	3.1 (0.9 to 10.6)	0.14 (0.00 to 0.28)	NS
Dizziness	1500 mg vs. 1000 mg	9/44	3/43	2.9 (0.9 to 10.1)	0.13 (-0.01 to 0.28)	NS
Dyspepsia	1000 mg vs. 500 mg	8/43	3/45	2.8 (0.8 to 9.8)	0.12 (-0.02 to 0.26)	NS
Dyspepsia	1500 mg vs. 500 mg	7/44	3/45	2.4 (0.7 to 8.6)	0.09 (-0.04 to 0.22)	NS
Dyspepsia	1500 mg vs. 1000 mg	7/44	8/43	0.9 (0.3 to 2.2)	-0.03 (-0.19 to 0.13)	NS
Infection	1000 mg vs. 500 mg	7/43	8/45	0.9 (0.4 to 2.3)	-0.01 (-0.17 to 0.14)	NS
Infection	1500 mg vs. 500 mg	9/44	8/45	1.2 (0.5 to 2.7)	0.03 (-0.14 to 0.19)	NS
Infection	1500 mg vs. 1000 mg	9/44	7/43	1.3 (0.5 to 3.1)	0.04 (-0.12 to 0.20)	NS

Appendix Table 137. Dose response in adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[44] (continued)

Adverse effect	Daily doses of divalproex	Events/ randomized with larger dose	Events/ randomized with smaller dose	Relative risk (95% CI)	Absolute risk difference (95% CI	Attributable events per 1000 treated (95% CI)
Nausea	**1000 mg vs. 500 mg**	**4/43**	**12/45**	**0.3 (0.1 to 1.0)**	**-0.17 (-0.33 to -0.02)**	**-174 (-329 to -18)**
Nausea	1500 mg vs. 500 mg	15/44	12/45	1.3 (0.7 to 2.4)	0.07 (-0.12 to 0.26)	NS
Nausea	**1500 mg vs. 1000 mg**	**15/44**	**4/43**	**3.7 (1.3 to 10.2)**	**0.25 (0.08 to 0.41)**	**248 (83 to 413)**
Pain	1000 mg vs. 500 mg	3/43	4/45	0.8 (0.2 to 3.3)	-0.02 (-0.13 to 0.09)	NS
Pain	1500 mg vs. 500 mg	5/44	4/45	1.3 (0.4 to 4.5)	0.02 (-0.10 to 0.15)	NS
Pain	1500 mg vs. 1000 mg	5/44	3/43	1.6 (0.4 to 6.4)	0.04 (-0.08 to 0.16)	NS
Somnolence	1000 mg vs. 500 mg	3/43	3/45	1.0 (0.2 to 4.9)	0.00 (-0.10 to 0.11)	NS
Somnolence	1500 mg vs. 500 mg	8/44	3/45	2.7 (0.8 to 9.6)	0.12 (-0.02 to 0.25)	NS
Somnolence	1500 mg vs. 1000 mg	8/44	3/43	2.6 (0.7 to 9.2)	0.11 (-0.03 to 0.25)	NS
Tremor	1000 mg vs. 500 mg	3/43	0/45	7.3 (0.4 to 137.6)	0.07 (-0.02 to 0.16)	NS
Tremor	**1500 mg vs. 500 mg**	**7/44**	**0/45**	**15.3 (0.9 to 260.6)**	**0.16 (0.05 to 0.27)**	**159 (46 to 272)**
Tremor	1500 mg vs. 1000 mg	7/44	3/43	2.3 (0.6 to 8.2)	0.09 (-0.04 to 0.22)	NS
Vomiting	1000 mg vs. 500 mg	2/43	2/45	1.0 (0.2 to 7.1)	0.00 (-0.09 to 0.09)	NS
Vomiting	1500 mg vs. 500 mg	5/44	2/45	2.6 (0.5 to 12.5)	0.07 (-0.04 to 0.18)	NS
Vomiting	1500 mg vs. 1000 mg	5/44	2/43	2.4 (0.5 to 11.9)	0.07 (-0.05 to 0.18)	NS

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D138. Treatment discontinuation due to bothersome adverse effects with valproate vs. placebo, results from moderate risk of bias randomized controlled clinical trials

Adverse effect that led to treatment discontinuation	Daily dose	Reference	Events/ randomized with valproate	Events/ randomized with placebo	Rate, % with valproate [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Discontinuations due to adverse effects	400 mg twice a day	Hering, 1992[46]	1/32	2/32	3.1[6.3]	0.5 (0.0 to 5.2)	-0.03 (-0.13 to 0.07)
Deterioration of migraine	**1000mg to 1500 mg per day**	Jensen, 1994[47]	**4/43**	**14/43**	**9.3[32.6]**	**0.3 (0.1 to 0.8)**	**-0.23 (-0.40 to -0.07)**
Nausea	1000mg to 1500 mg per day	Jensen, 1994[47]	3/43	0/43	7.0[0.0]	7.0 (0.4 to 131.6)	0.07 (-0.02 to 0.16)
Abdominal pain	1000mg to 1500 mg per day	Jensen, 1994[47]	0/43	1/43	0.0[2.3]	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Vertigo	1000mg to 1500 mg per day	Jensen, 1994[47]	2/43	0/43	4.7[0.0]	5.0 (0.2 to 101.2)	0.05 (-0.03 to 0.12)
Weight gain	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	1/43	2.3[2.3]	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)
Increased appetite	1000mg to 1500 mg per day	Jensen, 1994[47]	0/43	1/43	0.0[2.3]	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Dry mouth	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Tremor	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Total	1000mg to 1500 mg per day	Jensen, 1994[47]	4/43	2/43	9.3[4.7]	2.0 (0.4 to 10.4)	0.05 (-0.06 to 0.15)

Bold - significant difference at 95% confidence limit
CI – confidence interval

Appendix Table D139. Adverse effects with valproate vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trials

Adverse effects	Daily dose	Reference	Events/ randomized with valproate	Events/ randomized placebo	Rate,% with valproate [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abdominal pain	1000mg to 1500 mg per day	Jensen, 1994[47]	2/43	1/43	4.7[2.3]	2.0 (0.2 to 21.2)	0.02 (-0.05 to 0.10)
Constipation	400 mg twice a day	Hering, 1992[46]	0/32	1/32	0.0[3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Diarrhea	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Dizziness	400 mg twice a day	Hering, 1992[46]	0/32	1/32	0.0[3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Drowsiness	1000mg to 1500 mg per day	Jensen, 1994[47]	5/43	2/43	11.6[4.7]	2.5 (0.5 to 12.2)	0.07 (-0.04 to 0.18)
Dry mouth	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Dyspepsia	400 mg twice a day	Hering, 1992[46]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Dyspnea	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Increased appetite	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	1/43	2.3[2.3]	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)
Mild weariness	400 mg twice a day	Hering, 1992[46]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Nausea	1000mg to 1500 mg per day	Jensen, 1994[47]	5/43	2/43	11.6[4.7]	2.5 (0.5 to 12.2)	0.07 (-0.04 to 0.18)
Nausea	400 mg twice a day	Hering, 1992[46]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Pain in neck/shoulders	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Restless legs	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Tinnitus	1000mg to 1500 mg per day	Jensen, 1994[47]	0/43	1/43	0.0[2.3]	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Total	1000mg to 1500 mg per day	Jensen, 1994[47]	14/43	7/43	32.6[16.3]	2.0 (0.9 to 4.5)	0.16 (-0.02 to 0.34)
Tremor	1000mg to 1500 mg per day	Jensen, 1994[47]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Vertigo	1000mg to 1500 mg per day	Jensen, 1994[47]	3/43	0/43	7.0[0.0]	7.0 (0.4 to 131.6)	0.07 (-0.02 to 0.16)
Weight gain	1000mg to 1500 mg per day	Jensen, 1994[47]	3/43	1/43	7.0[2.3]	3.0 (0.3 to 27.7)	0.05 (-0.04 to 0.13)

CI – confidence interval

Appendix Table D140. Strength of evidence of treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials)

Active treatment	Control treatment	Reference	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Propranolol	Placebo	Diamond, 1976[48]	Moderate	Yes	Not applicable	No	Low
Divalproex	Propranolol	Kaniecki, 1997[66]	High	Yes	Not applicable	No	Insufficient
Propranolol	Nifedipine	Albers, 1989[72]	High	Yes	Not applicable	No	Insufficient
Propranolol	Acetylsalicylic acid	Baldrati, 1983[216]	Moderate	Yes	Not applicable	No	Low
Propranolol	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[102]	High	Yes	Not applicable	No	Insufficient
Propranolol + Amitriptyline	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[102]	High	Yes	Not applicable	No	Insufficient
Propranolol + Amitriptyline + Biofeedback	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[102]	High	Yes	Not applicable	No	Insufficient
Propranolol + Biofeedback	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[102]	High	Yes	Not applicable	No	Insufficient
Propranolol + Biofeedback	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[102]	High	Yes	Not applicable	No	Insufficient

Appendix Table D141. Treatment discontinuation due to adverse effects with beta-blocker timolol for migraine prevention in adults, results from individual randomized controlled clinical trials

Reference Risk of bias	Drug and dose	Outcome	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Stellar, 1984[76] Moderate	Timolol 10mg twice a day	Moderate chest pain on day 28 leading to discontinuation	1/47 [2.1%]	0/47 [0.0%]	3.0 (0.1 to 71.8)	0.02 (-0.04 to 0.1)
	Timolol 10mg twice a day	Discontinued therapy because of severe epigastric distress and fecal impaction	1/47 [2.1%]	0/47 [0.0%]	3.0 (0.1 to 71.8)	0.02 (-0.04 to 0.1)
	Timolol 10mg twice a day	Withdrew due to adverse experiences	2/47 [4.3%]	0/47 [0.0%]	5.0 (0.2 to 101.4)	0.04 (-0.03 to 0.1)

Appendix Table D142. Strength of evidence of treatment discontinuation due to adverse effects with beta-blocker timolol for migraine prevention in adults (evidence from randomized controlled clinical trials)

Reference	Drug	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Stellar, 1984[76]	Timolol	Moderate	Yes	Not applicable	No	Low

Appendix Table D143. Adverse effects with timolol 10mg twice a day (results from randomized controlled clinical trials pooled with random effects model)

Adverse effect	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with active placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Weights, random effects, inverse variance	Absolute risk difference (95% CI)	Weights, random effects, inverse variance
Dizziness	Tfelt-Hansen, 1984[58] Moderate	5/96	1/48	5.2 [2.1]	2.5 (0.3 to 20.8)	68.9	0.03 (-0.03 to 0.09)	74.99
Dizziness	Standnes, 1982[59] Moderate	1/25	0/25	4.0 [0.0]	3.0 (0.1 to 70.3)	31.1	0.04 (-0.06 to 0.14)	25.01
Dizziness	Pooled	6/121	1/73	5.0 [1.4]	2.6 (0.5 to 15.4)	100	0.03 (-0.02 to 0.09)	100
Heterogeneity	P value/I squared				0.93/0.00%		0.89/0.00%	
Nausea	Tfelt-Hansen, 1984[58] Moderate	2/96	1/48	2.1 [2.1]	1.0 (0.1 to 10.8)	63.51	0.00 (-0.05 to 0.05)	92.22
Nausea	Standnes, 1982[59] Moderate	0/25	1/13	0.0 [4.0]	0.2 (0.0 to 4.1)	36.49	-0.08 (-0.25 to 0.09)	7.78
Nausea	Pooled	2/121	2/61	1.7 [2.5]	0.5 (0.1 to 3.5)	100	-0.01 (-0.05 to 0.04)	100
Heterogeneity	P value/I squared				0.39/0.00%		0.39/0.00%	
Adverse effects	Tfelt-Hansen, 1984[58] Moderate	38/96	12/48	39.6 [24.0]	1.6 (0.9 to 2.8)	81.24	0.15 (0.00 to 0.31)	78.11
Adverse effects	Standnes, 1982[59] Moderate	8/25	3/13	32.0 [20.0]	1.4 (0.4 to 4.4)	18.76	0.09 (-0.20 to 0.38)	21.89
Adverse effects	Pooled	46/121	14/61	38.0 [23.1]	1.6 (1.0 to 2.6)	100	0.14 (0.00 to 0.28)	100
Heterogeneity	P value/I squared				0.81/0.00%		0.72/0.00%	

Appendix Table D144. Adverse effects with timolol 10mg twice a day (results from randomized controlled clinical trials)

Adverse effects	Reference Risk of bias	Events/randomized with active drug	Events/randomized with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abnormal dreaming	Tfelt-Hansen, 1984[58] Moderate	2/96	0/96	5.0 (0.2 to 102.8)	0.02 (-0.01 to 0.06)
Blurred vision	Standnes, 1982[59] Moderate	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Cold extremites	Standnes, 1982[59] Moderate	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Depression	Tfelt-Hansen, 1984[58] Moderate	2/96	0/96	5.0 (0.2 to 102.8)	0.02 (-0.01 to 0.06)
Dyspnea	Standnes, 1982[59] Moderate	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Fatigue/tiredness	Tfelt-Hansen, 1984[58] Moderate	18/96	8/48	1.1 (0.5 to 2.5)	0.02 (-0.11 to 0.15)
Gastroenteritis	Standnes, 1982[59] Moderate	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Increased weight	Standnes, 1982[59] Moderate	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Sleep disturbances	Tfelt-Hansen, 1984[58] Moderate	4/96	1/48	2.0 (0.2 to 17.4)	0.02 (-0.04 to 0.08)
Tiredness	Standnes, 1982[59] Moderate	6/25	2/13	1.6 (0.4 to 6.7)	0.09 (-0.17 to 0.34)

Appendix Table D145. Adverse effects with acetazolamide, 500 mg/day vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[77]

Adverse effect	Events/ randomized with acetazolamide	Events/ randomized with placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events (95% CI)
Paresthesia	**21/26**	**2/27**	**80.8[7.4]**	**10.9 (2.8 to 41.9)**	**0.73 (0.55 to 0.91)**	**1 (1 to 2)**	**734 (553 to 914)**
Fatigue, drowsiness, memory impairment, malaise, fasciculations	**15/26**	**4/27**	**57.7[14.8]**	**3.9 (1.5 to 10.2)**	**0.43 (0.20 to 0.66)**	**2 (2 to 5)**	**429 (196 to 661)**
Gastrointestinal intolerance	3/26	2/27	11.5[7.4]	1.6 (0.3 to 8.6)	0.04 (-0.12 to 0.20)		
Hypokalemia	1/26	0/27	3.8[0.0]	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.14)		
Hyperuricemia	1/26	0/27	3.8[0.0]	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.14)		
Skin eruption	0/26	2/27	0.0[7.4]	0.2 (0.0 to 4.1)	-0.07 (-0.19 to 0.04)		
Fever and shivering	0/26	1/27	0.0[3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)		
Dry mouth	1/26	1/27	3.8[3.7]	1.0 (0.1 to 15.7)	0.00 (-0.10 to 0.10)		
Breast tension	0/26	1/27	0.0[3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)		
Rhinitis	1/26	2/27	3.8[7.4]	0.5 (0.1 to 5.4)	-0.04 (-0.16 to 0.09)		
Tinnitus	0/26	1/27	0.0[3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)		
Miscellaneous	1/26	3/27	3.8[11.1]	0.3 (0.0 to 3.1)	-0.07 (-0.21 to 0.07)		

Bold - significant at 95% confidence limit
CI – confidence level

Appendix Table D146. Adverse effects with carbamazepine vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trial[83]

Adverse effect	Events/ randomized with active drug	Events/ randomized with placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm (95% CI)	Attributable events per 1000 treated (95% CI)
Drowsiness	**5/48**	**0/48**	**10.4 [0.0]**	**11.0 (0.6 to 193.6)**	**0.10 (0.01 to 0.20)**	**10 (5 to 88)**	104 (11 to 197)
Vertigo or giddiness	**23/48**	**2/48**	**47.9 [4.2]**	**11.5 (2.9 to 46.1)**	**0.44 (0.29 to 0.59)**	**2 (2 to 4)**	438 (285 to 590)
Total	**30/48**	**11/48**	**62.5 [22.9]**	**2.7 (1.6 to 4.8)**	**0.40 (0.21 to 0.58)**	**3 (2 to 5)**	396 (214 to 577)
Necessitating reduction of dosage	**6/48**	**0/48**	**12.5 [0.0]**	**13.0 (0.8 to 224.5)**	**0.13 (0.03 to 0.22)**	**8 (4 to 39)**	125 (26 to 224)
Nausea	4/48	3/48	8.3 [6.3]	1.3 (0.3 to 5.6)	0.02 (-0.08 to 0.12)		
Dry mouth	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)		
Heavy eyes	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)		
Constipation	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)		
Vomiting	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)		
Weight gain	1/48	1/48	2.1 [2.1]	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)		
Sweating	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)		
Transient rash	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)		
Dysuria	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)		
Blacked nose	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)		
Lack of drive	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)		
Flushing	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)		
Blunted feeling	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)		
Heavy head	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)		

Bold - significant at 95% confidence limit
CI – confidence level

Appendix Table D147. Adverse effects with gabapentin, titrated up to 2400 mg daily vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trial[78]

Adverse effect	Events/ randomized with active drug	Events/ randomized with placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm (95% CI)	Attributable Events per 1000 treated (95% CI)
Dizziness	**25/98**	**5/98**	**25.5 [11.1]**	**2.3 (0.9 to 5.6)**	**0.14 (0.02 to 0.27)**	**7 (4 to 56)**	**144 (18 to 270)**
Somnolence	**24/98**	**5/98**	**24.5 [11.1]**	**2.2 (0.9 to 5.4)**	**0.13 (0.01 to 0.26)**	**7 (4 to 117)**	**134 (9 to 259)**
Asthenia	22/98	12/98	22.4 [26.7]	0.8 (0.5 to 1.5)	-0.04 (-0.20 to 0.11)		
Infection	11/98	11/98	11.2 [24.4]	0.5 (0.2 to 1.0)	-0.13 (-0.27 to 0.01)		
Weight gain	3/98	1/98	3.1 [2.2]	1.4 (0.1 to 12.9)	0.01 (-0.05 to 0.06)		
Designated as probably, possibly, or definitely related to study drug (Total)	**66/98**	**22/98**	**67.3 [48.9]**	**1.4 (1.0 to 1.9)**	**0.18 (0.01 to 0.36)**	**5 (3 to 87)**	**185 (12 to 358)**

Bold - significant at 95% confidence limit
CI – confidence level

Appendix Table D148. Treatment discontinuation due to bothersome adverse effects with lamotrigine, titrated up to 200 mg daily vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[84]

Adverse effect	Events/ randomized with active drug	Events/ randomized with placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95%CI)	Number needed to treat to harm (95% CI)	Attributable Events per 1000 treated (95% CI)
Rash	**7/18**	**1/40**	**38.9[3]**	**15.6 (2.1 to 117.3)**	**0.36 (0.13 to 0.59)**	**3 (2 to 7)**	**364 (134 to 594)**
Dizziness	1/18	0/40	5.6[0]	6.5 (0.3 to 151.7)	0.06 (-0.07 to 0.18)		
Leukopenia	0/18	1/40	0.0[3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)		
Dyspepsia	0/18	1/40	0.0[3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)		
Nausea	0/18	1/40	0.0[3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)		
Other	2/18	1/40	11.1[3]	4.4 (0.4 to 45.9)	0.09 (-0.07 to 0.24)		
Any	**7/18**	**3/40**	**38.9[8]**	**5.2 (1.5 to 17.8)**	**0.31 (0.07 to 0.55)**	**3 (2 to 13)**	**314 (74 to 553)**

Bold- significant at 95% confidence limit
CI –confidence level

Appendix Table D149. Adverse effects with oxcarbazepine, titrated to a maximum tolerated dose of 1,200 mg/day vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[80]

Adverse effect	Events/ randomized with active drug	Events/ randomized with placebo	Rate, % with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm (95% CI)	Attributable Events per 1000 treated (95% CI)
Patients with any adverse effects	**68/85**	**55/85**	**80.0[64.7]**	**1.2 (1.0 to 1.5)**	**0.15 (0.02 to 0.29)**	**7 (4 to 49)**	**153 (20 to 285)**
Fatigue	**17/85**	**6/85**	**20.0[7.1]**	**2.8 (1.2 to 6.8)**	**0.13 (0.03 to 0.23)**	**8 (4 to 35)**	**129 (28 to 230)**
Dizziness	**15/85**	**6/85**	**17.6[7.1]**	**2.5 (1.0 to 6.1)**	**0.11 (0.01 to 0.20)**	**9 (5 to 121)**	**106 (8 to 204)**
Nausea	**14/85**	**4/85**	**16.5[4.7]**	**3.5 (1.2 to 10.2)**	**0.12 (0.03 to 0.21)**	**8 (5 to 37)**	**118 (27 to 208)**
Somnolence	7/85	6/85	8.2[7.1]	1.2 (0.4 to 3.3)	0.01 (-0.07 to 0.09)		
Balance disorder	5/85	2/85	5.9[2.4]	2.5 (0.5 to 12.5)	0.04 (-0.02 to 0.09)		
Insomnia	5/85	6/85	5.9[7.1]	0.8 (0.3 to 2.6)	-0.01 (-0.09 to 0.06)		
Migraine	5/85	2/85	5.9[2.4]	2.5 (0.5 to 12.5)	0.04 (-0.02 to 0.09)		
Paresthesia	5/85	1/85	5.9[1.2]	5.0 (0.6 to 41.9)	0.05 (-0.01 to 0.10)		
Sinusitis	2/85	5/85	2.4[5.9]	0.4 (0.1 to 2.0)	-0.04 (-0.09 to 0.02)		

Bold - significant at 95% confidence limit
CI – confidence level

Appendix Table D150. Strength of evidence of treatment discontinuation due to adverse effects with beta-blockers for migraine prevention in adults (evidence from randomized controlled clinical trials)

Reference	Drug	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Forssman, 1982[92] Forssman, 1983[93]	Atenolol	Moderate	Yes	Not applicable	No	Low
van de Ven, 1997[98]	Bisoprolol	Moderate	Yes	Not applicable	No	Low
Andersson, 1983[94]	Metoprolol	Moderate	Yes	Not applicable	No	Low
Freitag, 1984[95]	Nadolol	Low	Yes	Not applicable	No	Low
Sjaastad, 1972[86]	Pindolol (LB-46)	Moderate	Yes	Not applicable	No	Low

Appendix Table D151. Treatment discontinuation due to adverse effects with beta-blockers for migraine prevention in adults, results from individual randomized controlled clinical trials

Reference Risk of bias	Drug and dose	Outcome	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Johannsson, 1987[96] Moderate	Atenolol 100mg	Withdrawal due to side effects	0/72 [0.0%]	3/72 [4.2%]	0.1 (0.0 to 2.7)	-0.04 (-0.09 to 0.0)
Forssman, 1982[92] Forssman, 1983[93] Moderate	Atenolol 100mg/day	Withdrawal due to mood alternations and increased tiredness	1/24 [4.2%]	0/24 [0.0%]	3.0 (0.1 to 70.2)	0.04 (-0.07 to 0.1)
Forssman, 1982[92] Forssman, 1983[93] Moderate	Atenolol 100mg/day	Withdrawal due to intolerable increase of headache attack	0/24 [0.0%]	1/24 [4.2%]	0.3 (0.0 to 7.8)	-0.04 (-0.15 to 0.1)
van de Ven, 1997[98] Moderate	Bisoprolol 5mg/day Bisoprolol 10mg/day	Dropped out of the study due to adverse effects	4/74 [5.4%] 7/77 [9.1%]	2/37 [5.3%] 2/38 [5.3%]	1.0 (0.2 to 5.2) 1.7 (0.4 to 7.9)	0.00 (-0.09 to 0.1) 0.04 (-0.06 to 0.1)
Andersson, 1983[94] Moderate	Metoprolol 200mg/day thereafter	Discontinued due to side-effects	1/34 [2.9%]	1/37 [2.7%]	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.1)
Freitag, 1984[95] Low	Nadolol 80mg to 240mg/day	Discontinued due to bradycardia	1/24 [4.2%]	0/8 [0.0%]	1.1 (0.0 to 24.2)	0.04 (-0.13 to 0.2)
Sjaastad, 1972[86] Moderate	Pindolol (LB-46) 7.5 to 15mg	Discontinued due to side-effects	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)

Appendix Table D152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
Ekbom, 1975[87] Moderate	Alprenolol 200mg/day ("Durule")	Dizziness	1/33 [3.0%]	0/33 [0.0%]	3.0 (0.1 to 71.1)	0.03 (-0.05 to 0.1)		
	Alprenolol 200mg/day ("Durule")	Tiredness and dizziness	1/33 [3.0%]	0/33 [0.0%]	3.0 (0.1 to 71.1)	0.03 (-0.05 to 0.1)		
	Alprenolol 200mg/day ("Durule")	Perspiration	2/33 [6.1%]	0/33 [0.0%]	5.0 (0.2 to 100.3)	0.06 (-0.04 to 0.2)		
	Alprenolol 200mg/day ("Durule")	Dryness of the mouth	1/33 [3.0%]	0/33 [0.0%]	3.0 (0.1 to 71.1)	0.03 (-0.05 to 0.1)		
	Alprenolol 200mg/day ("Durule")	Retrosternal burning sensation on swallowing	3/33 [9.1%]	0/33 [0.0%]	7.0 (0.4 to 130.4)	0.09 (-0.02 to 0.2)		
Forssman, 1982[92] Forssman, 1983[93]	**Atenolol 100mg/day**	**Slight dizziness of orthostatic type during first week**	**6/24 [25.0%]**	**1/24 [4.2%]**	**6.0 (0.8 to 46.1)**	**0.21 (0.02 to 0.4)**	**5 (3 to 57)**	**208 (18 to 399)**
Forssman, 1982[92] Forssman, 1983[93]	Atenolol 100mg/day	Increased diffuse tiredness	2/24 [8.3%]	0/24 [0.0%]	5.0 (0.3 to 99.0)	0.08 (-0.05 to 0.2)		
van de Ven, 1997[98] Moderate	Bisoprolol 5mg/day	Fatigue	7/74 [9.5%]	3/37 [9.3%]	1.1 (0.3 to 4.1)	0.01 (-0.10 to 0.1)		
	Bisoprolol 10mg/day	Fatigue	9/77 [11.7%]	4/38 [9.3%]	1.1 (0.4 to 3.5)	0.01 (-0.10 to 0.1)		
	Bisoprolol 5mg/day	Dizziness	6/74 [8.1%]	2/37 [5.3%]	1.5 (0.3 to 7.1)	0.03 (-0.07 to 0.1)		
	Bisoprolol 10mg/day	Dizziness	5/77 [6.5%]	2/38 [5.3%]	1.2 (0.3 to 6.1)	0.01 (-0.08 to 0.1)		
Kangasneimi, 1987[97] Moderate	**Metoprolol 200mg once daily ("Durules")**	**Gastrointestinal side effects**	**16/77 [20.8%]**	**3/77 [3.9%]**	**5.3 (1.6 to 17.6)**	**0.17 (0.07 to 0.3)**	**6 (4 to 15)**	**169 (68 to 269)**
	Metoprolol 200mg once daily ("Durules")	**Fatigue/tiredness**	**13/77 [16.9%]**	**4/77 [5.2%]**	**3.3 (1.1 to 9.5)**	**0.12 (0.02 to 0.2)**	**9 (5 to 51)**	**117 (20 to 214)**

Appendix Table 152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
	Metoprolol 200mg once daily ("Durules")	Cardiovascular side effects	3/77 [3.9%]	3/77 [3.9%]	1.0 (0.2 to 4.8)	0.00 (-0.06 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	Sleep disturbances	4/77 [5.2%]	0/77 [0.0%]	9.0 (0.5 to 164.4)	0.05 (0.00 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	Other side effects	16/77 [20.8%]	15/77 [19.5%]	1.1 (0.6 to 2.0)	0.01 (-0.11 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	**Number of patients reporting side effects**	**43/77 [55.8%]**	**21/77 [27.3%]**	**2.0 (1.4 to 3.1)**	**0.29 (0.14 to 0.4)**	**3 (2 to 7)**	**286 (137 to 435)**
Andersson, 1983[94] Moderate	Metoprolol 200mg once daily ("Durules")	Sleep disturbances	4/34 [11.8%]	4/37 [10.8%]	1.1 (0.3 to 4.0)	0.01 (-0.14 to 0.2)		
	Metoprolol 200mg once daily ("Durules")	Fatigue	3/34 [8.8%]	0/37 [0.0%]	7.6 (0.4 to 142.0)	0.09 (-0.02 to 0.2)		
	Metoprolol 200mg once daily ("Durules")	Gastrointestinal	2/34 [5.9%]	2/37 [5.4%]	1.1 (0.2 to 7.3)	0.00 (-0.10 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	Bradycardia	2/34 [5.9%]	0/37 [0.0%]	5.4 (0.3 to 109.2)	0.06 (-0.03 to 0.2)		
	Metoprolol 200mg once daily ("Durules")	Paresthesia	0/34 [0.0%]	1/37 [2.7%]	0.4 (0.0 to 8.6)	-0.03 (-0.10 to 0.0)		
	Metoprolol 200mg once	Depression	1/34 [2.9%]	1/37 [2.7%]	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.1)		

Appendix Table 152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
	daily ("Durules")							
	Metoprolol 200mg once daily ("Durules")	Side effects (others)	0/34 [0.0%]	4/37 [10.8%]	0.1 (0.0 to 2.2)	-0.11 (-0.22 to 0.0)		
	Metoprolol 200mg once daily ("Durules")	Sleep disturbances	7/34 [20.6%]	5/37 [13.5%]	1.5 (0.5 to 4.3)	0.07 (-0.10 to 0.2)		
	Metoprolol 200mg once daily ("Durules")	**Fatigue**	**6/34 [17.6%]**	**1/37 [2.7%]**	**6.5 (0.8 to 51.5)**	**0.15 (0.01 to 0.3)**	**7 (3 to 90)**	**149 (11 to 288)**
	Metoprolol 200mg once daily ("Durules")	Gastrointestinal	1/34 [2.9%]	4/37 [10.8%]	0.3 (0.0 to 2.3)	-0.08 (-0.19 to 0.0)		
	Metoprolol 200mg once daily ("Durules")	Bradycardia	1/34 [2.9%]	1/37 [2.7%]	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	Paresthesia	0/34 [0.0%]	3/37 [8.1%]	0.2 (0.0 to 2.9)	-0.08 (-0.18 to 0.0)		
	Metoprolol 200mg once daily ("Durules")	Depression	1/34 [2.9%]	1/37 [2.7%]	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.1)		
	Metoprolol 200mg once daily ("Durules")	Side effects (others)	3/34 [8.8%]	6/37 [16.2%]	0.5 (0.1 to 2.0)	-0.07 (-0.23 to 0.1)		
Siniatchkin, 2007[99] Moderate	Metoprolol 200mg once daily ("Durules")	Tiredness	2/10 [20.0%]	1/10 [10.0%]	2.0 (0.2 to 18.7)	0.10 (-0.21 to 0.4)		

Appendix Table 152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
	Metoprolol 200mg once daily ("Durules")	Dizziness	1/10 [10.0%]	0/10 [0.0%]	3.0 (0.1 to 65.9)	0.10 (-0.14 to 0.3)		
	Metoprolol 200mg once daily ("Durules")	Cardiovascular problems	1/10 [10.0%]	0/10 [0.0%]	3.0 (0.1 to 65.9)	0.10 (-0.14 to 0.3)		
	Metoprolol 200mg once daily ("Durules")	Gastrointestinal disturbances	0/10 [0.0%]	2/10 [20.0%]	0.2 (0.0 to 3.7)	-0.20 (-0.48 to 0.1)		
Freitag, 1984[95] Low	Nadolol 80mg/day	Fatigue: moderate (on 80mg dose)	1/8 [12.5%]	0/8 [0.0%]	3.0 (0.1 to 64.3)	0.13 (-0.16 to 0.4)		
	Nadolol 80mg/day	Fatigue: moderate (on 40mg dose)	1/8 [12.5%]	0/8 [0.0%]	3.0 (0.1 to 64.3)	0.13 (-0.16 to 0.4)		
	Nadolol 160mg/day	Fatigue: mild (on 120mg dose)	1/8 [12.5%]	0/8 [0.0%]	3.0 (0.1 to 64.3)	0.13 (-0.16 to 0.4)		
	Nadolol 160mg/day	Fatigue: moderate(on 160mg dose)	1/8 [12.5%]	0/8 [0.0%]	3.0 (0.1 to 64.3)	0.13 (-0.16 to 0.4)		
	Nadolol 160mg/day	Bradycardia (45 bpm): Severe (on 120mg dose)	1/8 [12.5%]	0/8 [0.0%]	3.0 (0.1 to 64.3)	0.13 (-0.16 to 0.4)		
Ryan, 1982[90] Ryan, 1983[91] Moderate	Nadolol 240mg/day	Sweaty	1/20 [5.0%]	0/20 [0.0%]	3.0 (0.1 to 69.5)	0.05 (-0.08 to 0.2)		
	Nadolol 80mg/day	Tinnitus	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 160mg/day	Tinnitus	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 240mg/day	Tinnitus	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 80mg/day	Vertigo	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 160mg/day	Vertigo	2/20 [10.0%]	0/7 [0.0%]	1.9 (0.1 to 35.5)	0.10 (-0.12 to 0.3)		
	Nadolol 240mg/day	Vertigo	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		

Appendix Table 152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
	Nadolol 80mg/day	Kidney stone	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 160mg/day	Kidney stone	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 240mg/day	Kidney stone	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 80mg/day	Bloating	1/20 [5.0%]	0/7 [5.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 160mg/day	Bloating	1/20 [5.0%]	0/7 [5.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	Bloating	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 80mg/day	Drowsiness	3/20 [15.0%]	0/7 [5.0%]	2.7 (0.2 to 46.1)	0.15 (-0.08 to 0.4)		
	Nadolol 160mg/day	Drowsiness	1/20 [5.0%]	0/7 [5.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	Drowsiness	1/20 [5.0%]	0/7 [5.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	General weakness	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	Insomnia	2/20 [10.0%]	0/7 [0.0%]	1.9 (0.1 to 35.5)	0.10 (-0.12 to 0.3)		
	Nadolol 240mg/day	Nausea	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	Chest pain	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 80mg/day	Weak extremities	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 160mg/day	Weak extremities	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 240mg/day	Weak extremities	0/20 [0.0%]	0/7 [5.0%]	0.0 (0.0 to 0.0)	0.00 (-0.18 to 0.2)		
	Nadolol 160mg/day	Decreased sex	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
	Nadolol 240mg/day	Numbness: extremities	1/20 [5.0%]	0/7 [0.0%]	1.1 (0.1 to 25.2)	0.05 (-0.15 to 0.3)		
Sjaastad, 1972[86]	Pindolol (LB-	Nausea	3/28	0/28	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)		

Appendix Table 152. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Drug, dose	Adverse effect	Events/ randomized [Rate of outcome with drug, %]	Events/ randomized [Rate of outcome with placebo, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable Events per 1000 treated (95% CI)
Moderate	46) 7.5 to 15mg		[10.7%]	[0.0%]				
	Pindolol (LB-46) 7.5 to 15mg	Chest discomfort	1/28 [3.6%]	1/28 [3.6%]	1.0 (0.1 to 15.2)	0.00 (-0.10 to 0.1)		
	Pindolol (LB-46) 7.5 to 15mg	Lethargy	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)		
	Pindolol (LB-46) 7.5 to 15mg	**Dizziness/faintness (orthostatic)**	**6/28 [21.4%]**	**0/28 [0.0%]**	**13.0 (0.8 to 220.3)**	**0.21 (0.06 to 0.4)**	**5 (3 to 18)**	**214 (55 to 373)**
	Pindolol (LB-46) 7.5 to 15mg	Increased appetite with slight weight gain	1/28 [3.6%]	1/28 [3.6%]	1.0 (0.1 to 15.2)	0.00 (-0.10 to 0.1)		
	Pindolol (LB-46) 7.5 to 15mg	Single attacks worse	1/28 [3.6%]	0/28 [0.0%]	3.0 (0.1 to 70.6)	0.04 (-0.06 to 0.1)		
	Pindolol (LB-46) 7.5 to 15mg	50% reduction in headache indices	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)		
Stellar, 1984[76] Moderate	Timolol 10mg twice a day	Insomnia	7/47 [14.9%]	2/47 [4.3%]	3.5 (0.8 to 16.0)	0.11 (-0.01 to 0.2)		
	Timolol 10mg twice a day	Fatigue	3/47 [6.4%]	1/47 [2.1%]	3.0 (0.3 to 27.8)	0.04 (-0.04 to 0.1)		
	Timolol 10mg twice a day	Light-headedness	3/47 [6.4%]	2/47 [4.3%]	1.5 (0.3 to 8.6)	0.02 (-0.07 to 0.1)		

Bold - significant differences at 95% CI

Appendix Table D153. Comparative safety of topiramate vs. botox for migraine prevention in adults (results from individual randomized controlled clinical trials)

Adverse effects	Reference Risk of bias	Events/ randomized with topiramate	Events/ randomized with botox	Relative risk (95% CI)	Absolute risk difference (95% CI)
Nausea	Cady, 2011[159] Moderate	6/30	13/29	0.4 (0.2 to 1.0)	**-0.25 (-0.48 to -0.02)**
Mood swing	Cady, 2011[159] Moderate	6/30	4/29	1.5 (0.5 to 4.6)	0.06 (-0.13 to 0.25)
Difficulty concentrating or with memory	Cady, 2011[159] Moderate	11/30	13/29	0.8 (0.4 to 1.5)	-0.08 (-0.33 to 0.17)
Mild fatigue	Cady, 2011[159] Moderate	15/30	16/29	0.9 (0.6 to 1.5)	-0.05 (-0.31 to 0.20)
Coginitive deficits (probable)	Mathew, 2009[157] High	0/30	0/30	0.0 (0.0 to 0.0)	0.00 (0.00 to 0.00)
Dry mouth/thirst (definite)	Mathew, 2009[157] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Sleepiness/tiredness/fatigue/dizziness (probable)	Mathew, 2009[157] High	1/30	1/30	1.0 (0.1 to 15.3)	0.00 (-0.09 to 0.09)
Depression/mood disturbance (probable)	Mathew, 2009[157] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Appetite/weight loss (probable)	Mathew, 2009[157] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Night sweats (probable)	Mathew, 2009[157] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Night sweats (definite)	Mathew, 2009[157] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Blurred vision/vision problems (definite)	Mathew, 2009[157] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Blurred vision/vision problems (probable)	Mathew, 2009[157] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Sleepiness/tiredness/fatigue/dizziness (definite)	Mathew, 2009[157] High	3/30	2/30	1.5 (0.3 to 8.3)	0.03 (-0.11 to 0.17)
Dry mouth/thirst (probable)	Mathew, 2009[157] High	3/30	0/30	7.0 (0.4 to 129.9)	0.10 (-0.02 to 0.22)
Depression/mood disturbance (definite)	Mathew, 2009[157] High	5/30	0/30	11.0 (0.6 to 190.5)	**0.17 (0.03 to 0.31)**
Appetite/weight loss (definite)	Mathew, 2009[157] High	8/30	0/30	17.0 (1.0 to 281.9)	**0.27 (0.10 to 0.43)**
Paresthesias (probable)	Mathew, 2009[157] High	11/30	0/30	23.0 (1.4 to 373.5)	**0.37 (0.19 to 0.54)**

Appendix Table 153. Comparative safety of topiramate vs. botox for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse effects	Reference Risk of bias	Events/ randomized with topiramate	Events/ randomized with botox	Relative risk (95% CI)	Absolute risk difference (95% CI)
Paresthesias (definite)	Mathew, 2009[157] High	14/30	3/30	4.7 (1.5 to 14.6)	**0.37 (0.16 to 0.57)**
Coginitive deficits (definite)	Mathew, 2009[157] High	15/30	0/30	31.0 (1.9 to 495.6)	**0.50 (0.32 to 0.68)**
Drug-related adverse effects	Mathew, 2009[157] High	25/30	18/30	1.4 (1.0 to 1.9)	**0.23 (0.01 to 0.45)**
Probable/possible drug-related	Mathew, 2009[157] High	26/30	22/30	1.2 (0.9 to 1.5)	0.13 (-0.07 to 0.33)
All	Mathew, 2009[157] High	28/30	26/30	1.1 (0.9 to 1.3)	0.07 (-0.08 to 0.22)

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D154. Comparative safety of divalproex sodium vs. botox for migraine prevention in adults (results from a single moderate risk of bias randomized controlled clinical trial)[160]

Adverse effect	Events/ randomized with divalproex	Events/ randomized with botox	Relative risk (95% CI)	Absolute risk difference (95% CI)
Ptosis, eyelid (possibly related to treatment)	0/29	8/30	0.1 (0.0 to 1.0)	**-0.27 (-0.43 to -0.10)**
Ptosis, eyebrow (possibly related to treatment)	0/29	5/30	0.1 (0.0 to 1.6)	**-0.17 (-0.31 to -0.02)**
Headache intensity/frequency increase (possibly related to treatment)	0/29	2/30	0.2 (0.0 to 4.1)	-0.07 (-0.17 to 0.04)
Vision disturbance (possibly related to treatment)	2/29	1/30	2.1 (0.2 to 21.6)	0.04 (-0.08 to 0.15)
Dizziness (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Infection, viral (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Numbness (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Pruritis (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Tinnitus (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Tremors (possibly related to treatment)	3/29	0/30	7.2 (0.4 to 134.2)	0.10 (-0.02 to 0.23)
Other gastrointestinal discomfort (possibly related to treatment)	3/29	0/30	7.2 (0.4 to 134.2)	0.10 (-0.02 to 0.23)
Sleepiness (possibly related to treatment)	4/29	0/30	9.3 (0.5 to 165.4)	0.14 (0.00 to 0.27)
Weight gain (possibly related to treatment)	4/29	1/30	4.1 (0.5 to 34.9)	0.10 (-0.04 to 0.25)
Fatigue (possibly related to treatment)	5/29	0/30	11.4 (0.7 to 196.7)	**0.17 (0.03 to 0.32)**
Hair loss (possibly related to treatment)	5/29	1/30	5.2 (0.6 to 41.6)	0.14 (-0.01 to 0.29)
Nausea (possibly related to treatment)	9/29	1/30	9.3 (1.3 to 68.9)	**0.28 (0.10 to 0.46)**
Related to treatment	18/29	12/30	1.6 (0.9 to 2.6)	0.22 (-0.03 to 0.47)
Possibly related to treatment	22/29	15/30	1.5 (1.0 to 2.3)	**0.26 (0.02 to 0.50)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D155. Comparative safety of amitriptyline vs. botulinum toxin type A for migraine prevention in adults (results from a single high risk of bias randomized controlled clinical trial)[158]

Adverse effect	Events/ randomized with amitriptyline	Events/ randomized with botulinum	Relative risk (95% CI)	Absolute risk difference (95% CI)
Constipation	14/37	0/35	27.5 (1.7 to 443.8)	**0.38 (0.22 to 0.54)**
Dry mouth	16/37	5/35	3.0 (1.2 to 7.4)	**0.29 (0.09 to 0.49)**
Somnolence	19/37	1/35	18.0 (2.5 to 127.2)	**0.48 (0.31 to 0.66)**
Weight gain	22/37	4/35	5.2 (2.0 to 13.6)	**0.48 (0.29 to 0.67)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D156. Adverse effects leading to treatment discontinuation with topiramate vs. other drugs for migraine prevention in adults

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Aggravation of migraine leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	0/178 [0.0]	3/169 [1.8]	0.1 (0.0 to 2.6)	-0.02 (-0.04 to 0.00)
Anxiety leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	3/178 [1.7]	0/169 [0.0]	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Confusion leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	3/178 [1.7]	0/169 [0.0]	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Dizziness leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	3/178 [1.7]	0/169 [0.0]	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Dry mouth leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were	Dodick, 2009[169] Low	0/178 [0.0]	3/169 [1.8]	0.1 (0.0 to 2.6)	-0.02 (-0.04 to 0.00)

Appendix Table 156. Adverse effects leading to treatment discontinuation with topiramate vs. other drugs for migraine prevention in adults (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	were made up to 50mg BID (or the maximum tolerated dose))	made up to 50mg BID (or the maximum tolerated dose))					
Fatigue leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	6/178 [3.4]	4/169 [2.4]	1.4 (0.4 to 5.0)	0.01 (-0.03 to 0.05)
Hypoesthesia leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	3/178 [1.7]	0/169 [0.0]	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Somnolence leading to withdrawal	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**0/178 [0.0]**	**7/169 [4.1]**	**0.1 (0.0 to 1.1)**	**-0.04 (-0.07 to -0.01)**
Weight increase leading to withdrawal	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	0/178 [0.0]	8/169 [4.7]	0.1 (0.0 to 1.0)	**-0.05 (-0.08 to -0.01)**
Withdrew due to drowsiness	Topiramate 75mg/day (25mg in the morning and 50mg in	Valproate (slow-release) 750mg/day (250mg in	Bartolini, 2005[162] High	2/22 [9.1]	3/22 [13.6]	0.7 (0.1 to 3.6)	-0.05 (-0.23 to 0.14)

Appendix Table 156. Adverse effects leading to treatment discontinuation with topiramate vs. other drugs for migraine prevention in adults (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	the evening)	the morning and 500mg in the evening)					
Left the study due to impaired concentration	Topiramate 25mg/day, gradually titrated up to 100mg/day	Zonasamide 50mg/day, gradually titrated up to 200mg/day	Mohammadianinejad, 2011[170] Moderate	0/40 [0.0]	1/40 [2.5]	0.3 (0.0 to 7.9)	-0.03 (-0.09 to 0.04)
Left the study due to intolerable paresthesia	Topiramate 25mg/day, gradually titrated up to 100mg/day	Zonasamide 50mg/day, gradually titrated up to 200mg/day	Mohammadianinejad, 2011[170] Moderate	2/40 [5.0]	0/40 [0.0]	5.0 (0.2 to 101.0)	0.05 (-0.03 to 0.13)
Left the study due to unbearable restless leg syndrome	Topiramate 25mg/day, gradually titrated up to 100mg/day	Zonasamide 50mg/day, gradually titrated up to 200mg/day	Mohammadianinejad, 2011[170] Moderate	0/40 [0.0]	1/40 [2.5]	0.3 (0.0 to 7.9)	-0.03 (-0.09 to 0.04)

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D157. Discontinuation due to treatment failure with topiramate versus other drugs for migraine prevention in adults

Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	2/178 [1.1]	0/169 [0.0]	4.7 (0.2 to 98.2)	0.01 (-0.01 to 0.03)
Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	1/60 [1.7]	1/60 [1.7]	1.0 (0.1 to 15.6)	0.00 (-0.05 to 0.05)

CI – confidence interval

Appendix Table D158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abnormal vision	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	9/178 [5.1]	9/169 [5.3]	0.9 (0.4 to 2.3)	0.00 (-0.05 to 0.04)
Anorexia	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	12/178 [6.7]	8/169 [4.7]	1.4 (0.6 to 3.4)	0.02 (-0.03 to 0.07)
Anorexia	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	1/60 [1.7]	1/60 [1.7]	1.0 (0.1 to 15.6)	0.00 (-0.05 to 0.05)
Constipation	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	6/178 [3.4]	14/169 [8.3]	0.4 (0.2 to 1.0)	-0.05 (-0.10 to 0.00)
Constipation	Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[167] Moderate	0/24 [0.0]	13/28 [45.4]	0.0 (0.0 to 0.7)	-0.46 (-0.65 to -0.27)
Coughing	Topiramate 100mg (The starting dosage was 25mg/d for	Amitriptyline 100mg (The starting dosage was 25mg/d for	Dodick, 2009[169] Low	9/178 [5.1]	7/169 [4.1]	1.2 (0.5 to 3.2)	0.01 (-0.03 to 0.05)

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Difficulty with concentration/attention	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	12/178 [6.7]	5/169 [3.0]	2.3 (0.8 to 6.3)	0.04 (-0.01 to 0.08)
Distal paresthesias	**Topiramate 100mg BD**	**Levetiracetam 1000mg BD**	de Tommaso, 2007[165] **Moderate**	**7/13 [53.8]**	**0/15 [0.0]**	**17.1 (1.1 to 274.0)**	**0.54 (0.26 to 0.81)**
Dizziness	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	15/178 [8.4]	18/169 [10.7]	0.8 (0.4 to 1.5)	-0.02 (-0.08 to 0.04)
Drowsiness	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[165] Moderate	3/13 [23.1]	0/15 [0.0]	8.0 (0.5 to 141.8)	0.23 (-0.01 to 0.47)
Dry mouth	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**12/178 [6.7]**	**60/169 [35.5]**	**0.2 (0.1 to 0.3)**	**-0.29 (-0.37 to -0.21)**
Dyspepsia	Topiramate 100mg (The starting dosage was 25mg/d for	Amitriptyline 100mg (The starting dosage was 25mg/d for	Dodick, 2009[169] Low	9/178 [5.1]	14/169 [8.3]	0.6 (0.3 to 1.4)	-0.03 (-0.08 to 0.02)

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Fatigue	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	30/178 [16.9]	41/169 [24.3]	0.7 (0.5 to 1.1)	-0.07 (-0.16 to 0.01)
Gastrointestinal intolerance	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Giddiness	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	2/60 [3.3]	2/60 [3.3]	1.0 (0.1 to 6.9)	0.00 (-0.06 to 0.06)
Hair loss	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[163] Moderate	0/32 [0.0]	1/32 [3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Headache	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	9/178 [5.1]	0/169 [0.0]	18.0 (1.1 to 307.6)	0.05 (0.02 to 0.08)
Hyperosmia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	Keskinbora, 2008[167] **Moderate**	**0/24 [0.0]**	**15/28 [54.6]**	**0.0 (0.0 to 0.6)**	**-0.54 (-0.73 to -0.35)**
Hypoesthesia	**Topiramate 100mg (The starting**	**Amitriptyline 100mg (The starting**	Dodick, 2009[169] **Low**	**19/178 [10.7]**	**6/169 [3.6]**	**3.0 (1.2 to 7.3)**	**0.07 (0.02 to 0.12)**

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	**dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**					
Nausea	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made upto 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	18/178 [10.1]	12/169 [7.1]	1.4 (0.7 to 2.9)	0.03 (-0.03 to 0.09)
Palpitations	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	0/60 [0.0]	0/60 [0.0]	0.0 (0.0 to 0.0)	0.00 (-0.03 to 0.03)
Paresthesia	Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[167] Moderate	4/24 [15.0]	0/28 [0.0]	10.4 (0.6 to 184.6)	0.17 (0.01 to 0.32)
Paresthesia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	Keskinbora, 2008[167] **Moderate**	**8/24 [35.0]**	**0/28 [0.0]**	**19.7 (1.2 to 324.8)**	**0.33 (0.14 to 0.52)**
Paresthesia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a**	Keskinbora, 2008[167] **Moderate**	**10/24 [40.0]**	**0/28 [0.0]**	**24.4 (1.5 to 395.1)**	**0.42 (0.22 to 0.62)**

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	maximum dose of 200mg)	**maximum dose of 150mg/day)**					
Paresthesia	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**53/178 [29.8]**	**8/169 [4.7]**	**6.3 (3.1 to 12.8)**	**0.25 (0.18 to 0.32)**
Paresthesia	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[163] Moderate	3/32 [9.4]	0/32 [0.0]	7.0 (0.4 to 130.3)	0.09 (-0.02 to 0.21)
Paresthesia	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Paresthesia	**Topiramate 25mg/day, gradually titrated up to 100mg/day**	**Zonasamide 50mg/day, gradually titrated up to 200mg/day**	**Mohammadianinejad, 2011[170] Moderate**	**9/40 [22.5]**	**0/40 [0.0]**	**19.0 (1.1 to 315.8)**	**0.23 (0.09 to 0.36)**
Paresthesia and weight loss	**Topiramate 50mg (25mg daily increment over 1 week to 50mg)**	**Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)**	Shaygannejad, 2006[163] **Moderate**	**8/32 [25.0]**	**0/32 [0.0]**	**17.0 (1.0 to 282.7)**	**0.25 (0.10 to 0.40)**
Pharyngitis	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	8/178 [4.5]	11/169 [6.5]	0.7 (0.3 to 1.7)	-0.02 (-0.07 to 0.03)
Rash	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	0/60 [0.0]	2/60 [3.3]	0.2 (0.0 to 4.1)	-0.03 (-0.09 to 0.02)
Sedation and dizziness in the first days of therapy	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[165] Moderate	0/13 [0.0]	5/15 [33.3]	0.1 (0.0 to 1.7)	-0.33 (-0.59 to -0.08)

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Sinusitis	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	14/178 [7.9]	18/169 [10.7]	0.7 (0.4 to 1.4)	-0.03 (-0.09 to 0.03)
Sleepiness and concentraton difficulty	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Somnolence	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	21/178 [11.8]	30/169 [17.8]	0.7 (0.4 to 1.1)	-0.06 (-0.13 to 0.02)
Somnolence	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[163] Moderate	0/32 [0.0]	1/32 [3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Taste perversion	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	10/178 [5.6]	6/169 [3.6]	1.6 (0.6 to 4.3)	0.02 (-0.02 to 0.06)
Upper respiratory tract infection	Topiramate 100m g(The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	14/178 [7.9]	11/169 [6.5]	1.2 0.6 to 2.6)	0.01 (-0.04 to 0.07)

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Viral infection	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	14/178 [7.9]	11/169 [6.5]	1.2 (0.6 to 2.6)	0.01 (-0.04 to 0.07)
Weight gain	Topiramate 200mg(Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[167] Moderate	0/24 [0.0]	8/28 [27.3]	0.1 (0.0 to 1.1)	**-0.29 (-0.46 to -0.11)**
Weight gain	**Topiramate 50mg (25mg daily increment over 1 week to 50mg)**	**Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)**	Shaygannejad, 2006[163] **Risk of bias Moderate**	**0/32 [0.0]**	**11/32 [34.4]**	**0.0 (0.0 to 0.7)**	**-0.34 (-0.51 to -0.18)**
Weight increase	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**0/178 [0.0]**	**23/169 [13.6]**	**0.0 (0.0 to 0.3)**	**-0.14 (-0.19 to -0.08)**
Weight loss	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[163]Moderate	6/32 [18.8]	0/32 [0.0]	13.0 (0.8 to 221.5)	**0.19 (0.05 to 0.33)**
Weight loss	**Topiramate 100mg BD**	**Levetiracetam 1000mg BD**	de Tommaso, 2007[165] **Moderate**	**8/13 [61.5]**	**0/15 [0.0]**	**19.4 (1.2 to 307.1)**	**0.62 (0.35 to 0.89)**
<1% decrease to <1% increase from baseline	Topiramate 100mg (The starting dosage was 25mg/d for	Amitriptyline 100mg (The starting dosage was 25mg/d for	Dodick, 2009[169] Risk of bias Low	33/178 [18.7]	28/169 [16.5]	1.1 (0.7 to 1.8)	0.02 (-0.06 to 0.10)

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
≥1% loss of body weight during the study	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**115/178 [64.4]**	**32/169 [19.0]**	**3.4 (2.5 to 4.7)**	**0.46 (0.36 to 0.55)**
≥1% to <5% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made u to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**61/178 [34.5]**	**27/169 [15.8]**	**2.1 (1.4 to 3.2)**	**0.18 (0.09 to 0.27)**
≥1% to 5% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**23/178 [12.9]**	**61/169 [36.1]**	**0.4 (0.2 to 0.6)**	**-0.23 (-0.32 to -0.14)**
≥10% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the**	Dodick, 2009[169] **Low**	**1/178 [0.6]**	**15/169 [8.9]**	**0.1 (0.0 to 0.5)**	**-0.08 (-0.13 to -0.04)**

Appendix Table 158. Comparative safety effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse effect	Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
	maximum tolerated dose))	**maximum tolerated dose))**					
≥10% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made u pto 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**16/178 [8.8]**	**0/169 [0.0]**	**31.3 (1.9 to 518.3)**	**0.09 (0.05 to 0.13)**
≥5% loss of body weight during the study	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**53/178 [29.9]**	**5/169 [3.2]**	**10.1 (4.1 to 24.6)**	**0.27 (0.20 to 0.34)**
≥5% to 10% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**6/178 [3.5]**	**33/169 [19.6]**	**0.2 (0.1 to 0.4)**	**-0.16 (-0.23 to -0.10)**
≥5% to <10% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made u pto 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[169] **Low**	**38/178 [21.1]**	**5/169 [3.2]**	**7.2 (2.9 to 17.9)**	**0.18 (0.12 to 0.25)**

Bold - significant differences at 95% confidence limit; CI – confidence interval

Appendix Table D159. Risk of any adverse effects with topiramate vs. other drugs for migraine prevention in adults

Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	**Keskinbor, 2008[167] Moderate**	**9/23 [39.1]**	**22/28 [78.6]**	**0.5 (0.3 to 0.9)**	**-0.39 (-0.65 to -0.14)**
Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbor, 2008[167] Moderate	15/24 [62.5]	22/28 [78.6]	0.8 (0.6 to 1.1)	-0.16 (-0.41 to 0.09)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	121/178 [68.0]	128/169 [75.7]	0.9 (0.8 to 1.0)	-0.08 (-0.17 to 0.02)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	152/178 [85.4]	150/169 [88.8]	1.0 (0.9 to 1.0)	-0.03 (-0.10 to 0.04)
Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Keskinbora, 2008[167] Moderate	15/24 [62.5]	9/23 [39.1]	1.6 (0.9 to 2.9)	0.23 (-0.04 to 0.51)

Bold - significant difference at 95% confidence limit
CI – confidence interval

Appendix Table D160. All adverse effects leading to treatment discontinuation with topiramate vs. other drugs for migraine prevention in adults

Topiramate, Daily dose	Control drug, Daily dose	Reference Risk of bias	Events/ randomized [rate, %] with topiramate	Events/ randomized [rate, %] with control drug	Relative risk (95% CI)	Absolute risk difference (95% CI)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[169] Low	35/178 [19.7]	38/169 [22.5]	0.9 (0.6 to 1.3)	-0.03 (-0.11 to 0.06)
Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[167] Moderate	1/23 [4.3]	4/28 [14.3]	0.3 (0.0 to 2.5)	-0.10 (-0.25 to 0.05)
Topiramate 200mg(Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[167] Moderate	2/24 [8.3]	4/28 [14.3]	0.6 (0.1 to 2.9)	-0.06 (-0.23 to 0.11)
Topiramate 200mg(Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Keskinbora, 2008[167] Moderate	2/24 [8.3]	1/23 [4.3]	1.9 (0.2 to 19.7)	0.04 (-0.10 to 0.18)
Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[164] Low	3/60 [5.0]	3/60 [5.0]	1.0 (0.2 to 4.8)	0.00 (-0.08 to 0.08)
Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[165] Moderate	1/13 [7.7]	0/15 [0.0]	3.4 (0.2 to 77.6)	0.08 (-0.11 to 0.26)

CI – confidence interval

Appendix Table D161. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials)

Active treatment	Control treatment	Reference Risk of bias	Events/ randomized with active treatment	Events/ randomized with control treatment	Rate, % with active [control] treatment	Relative risk (95% CI)	Absolute risk difference (95% CI)
Propranolol 80 or 160 mg	Placebo	Diamond, 1976[48] Risk of bias Moderate	6/0	1/0	7 [1]	6.0 (0.7 to 48.8)	0.06 (0.00 to 0.12)
Divalproex Mean dose: 1414mg/d (Titrated to 1500 mg/d in 23 patients, to 2000mg/d in 2, downward to 1000mg/d in 6, and downward to 750mg/d in 1)	Propranolol Mean dose: 174mg/d (Titrated to 180 mg/d in 28 patients, to 240mg/d in 1, to 120 mg/d in 2, and to 60 mg/d in 1)	Kaniecki, 1997[66] Risk of bias High	4/37	1/37	11 [3]	4.0 (0.5 to 34.1)	0.08 (-0.03 to 0.19)
Propranolol 60 mg TID	**Nifedipine 30 mg TID**	**Albers, 1989[72] Risk of bias High**	**5/20**	**13/20**	**25 [65]**	**0.4 (0.2 to 0.9)**	**-0.40 (-0.68 to -0.12)**
Propranolol Mean dosage: 1.8 mg/kg/day	Acetylsalicylic acid Mean dosage: 13.5 mg/kg/day	Baldrati, 1983[216] Risk of bias Moderate	2/18	3/18	11 [17]	0.8 (0.3 to 2.4)	-0.12 (-0.58 to 0.35)
Propranolol 160 mg	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[102] Risk of bias High	1/44	4/45	2 [9]	0.3 (0.0 to 2.2)	-0.07 (-0.16 to 0.03)
Propranolol 160 mg	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was	Mathew, 1981[102] Risk of bias High	3/48	9/49	6 [18]	0.3 (0.1 to 1.2)	-0.12 (-0.25 to 0.01)

Appendix Table D161. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Active treatment	Control treatment	Reference Risk of bias	Events/ randomized with active treatment	Events/ randomized with control treatment	Rate, % with active [control] treatment	Relative risk (95% CI)	Absolute risk difference (95% CI)
	restricted to 6 mg a week.						
Propranolol + Amitriptyline Propranolol: 160 mg; Amitriptyline: 75 mg	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[102] Risk of bias High	2/41	4/45	5 [9]	0.5 (0.1 to 2.8)	-0.04 (-0.15 to 0.07)
Propranolol + Amitriptyline Propranolol: 160 mg; Amitriptyline: 75 mg	**Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.**	**Mathew, 1981[102] Risk of bias High**	**2/47**	**9/49**	**4 [18]**	**0.2 (0.1 to 1.0)**	**-0.14 (-0.26 to -0.02)**
Propranolol + Amitriptyline + Biofeedback Propranolol: 160 mg; Amitriptyline: 75 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[102] Risk of bias High	4/46	9/49	9 [18]	0.5 (0.2 to 1.4)	-0.10 (-0.23 to 0.04)
Propranolol + Amitriptyline + Biofeedback Propranolol: 160 mg;	Abortive treatment with ergotamine and analgesics	Mathew, 1981[102] Risk of bias High	3/38	4/45	8 [9]	0.9 (0.2 to 3.7)	-0.01 (-0.13 to 0.11)

Appendix Table D161. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Active treatment	Control treatment	Reference Risk of bias	Events/ randomized with active treatment	Events/ randomized with control treatment	Rate, % with active [control] treatment	Relative risk (95% CI)	Absolute risk difference (95% CI)
Amitriptyline: 75 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	(control) Total ergotamine intake was restricted to 6 mg a week.						
Propranolol + Biofeedback Propranolol: 160 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[102] Risk of bias High	2/39	4/45	5 [9]	0.6 (0.1 to 3.0)	-0.04 (-0.15 to 0.07)
Propranolol + Biofeedback Propranolol: 160 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[102] Risk of bias High	3/43	9/49	7 [18]	0.4 (0.1 to 1.3)	-0.11 (-0.25 to 0.02)

Bold-significant at 95% confidence limit
CI – confidence interval

Appendix Table D162. Comparative effectiveness and safety of beta-blockers combined with behavioral therapy (orientation + relaxation training; migraine warning signs and triggers; effectively using migraine medication and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. beta-blockers alone for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[192]

Definition of the outcome	Active treatment	Control treatment	Events randomized with active treatment	Events/ randomized with control treatment	Rate in active group,% [control group]	Relative risk (95%CI)	Absolute risk difference (95%CI)
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Placebo	Propranolol/nadolol	19/55	18/53	34.5 [34.0]	1.0 (0.6 to 1.7)	0.01 (-0.17 to 0.18)
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + Propranolol/nadolol**	**Propranolol/nadolol**	**53/69**	**18/53**	**76.8 [34.0]**	**2.3 (1.5 to 3.4)**	**0.43 (0.27 to 0.59)**
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + placebo**	**Behavioral migraine management + Propranolol/nadolol**	**19/55**	**53/69**	**34.5 [76.8]**	**0.4 (0.3 to 0.7)**	**-0.42 (-0.58 to -0.26)**
Dropped out	Behavioral migraine management + Placebo	Propranolol/nadolol	22/55	27/53	40.0 [50.9]	0.8 (0.5 to 1.2)	-0.11 (-0.30 to 0.08)
Dropped out	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	24/69	27/53	34.8 [50.9]	0.7 (0.4 to 1.0)	-0.16 (-0.34 to 0.01)
Dropped out	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	22/55	24/69	40.0 [34.8]	1.2 (0.7 to 1.8)	0.05 (-0.12 to 0.22)
Dropped due to side - effects	Behavioral migraine management + Placebo	Propranolol/nadolol	5/55	7/53	9.1 [13.2]	0.7 (0.2 to 2.0)	-0.04 (-0.16 to 0.08)
Dropped due to side - effects	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	6/69	7/53	8.7 [13.2]	0.7 (0.2 to 1.8)	-0.05 (-0.16 to 0.07)
Dropped out due to side effects	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	5/55	6/69	9.1 [8.7]	1.0 (0.3 to 3.2)	0.00 (-0.10 to 0.10)

Appendix Table 162. Comparative effectiveness and safety of beta-blockers combined with behavioral therapy (orientation +relaxation training; migraine warning signs and triggers; effectively using migraine medication, and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. beta-blockers alone for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[191] (continued)

Definition of the outcome	Active treatment	Control treatment	Events randomized with active treatment	Events/ randomized with control treatment	Rate in active group,% [control group]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Dropped due to lack of efficacy	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	1/69	5/53	1.4 [9.4]	0.2 (0.0 to 1.3)	-0.08 (-0.16 to 0.00)
Dropped due to lack of efficacy	Behavioral migraine management + Placebo	Propranolol/nadolol	4/55	5/53	7.3 [9.4]	0.8 (0.2 to 2.7)	-0.02 (-0.13 to 0.08)
Dropped out due to lack of efficacy	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	4/55	1/69	7.3 [1.4]	5.0 (0.6 to 43.6)	0.06 (-0.02 to 0.13)

Bold - significant at 95% confidence limit
CI – confidence interval

Appendix Table D163. Headache specific locus of control at month 16 beta-blockers combined with behavioral therapy (orientation + relaxation training; migraine warning signs and triggers; effectively using migraine medication and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. beta-blockers alone for migraine prevention in adults, results from individual moderate risk of bias randomized controlled clinical trial[191]

Outcome	Active	Control	Randomized for active [control] treatment	Mean [standard deviation] with active treatment	Mean [standard deviation] with control treatment	Mean difference (95% CI)	Standardized mean difference (95% CI)
Mean Change HSLC (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**21.4 [6.9]**	**26.4 [9.0]**	**-5.0 (-8.0 to -2.0)**	**-0.6 (-1.0 to -0.2)**
Mean Change HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**21.1 [8.4]**	**26.4 [9.0]**	**-5.3 (-8.4 to -2.2)**	**-0.6 (-1.0 to -0.2)**
Mean Change Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	21.4 [6.9]	21.1 [8.4]	0.3 (-2.4 to 3.0)	0.0 (-0.3 to 0.4)
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	Placebo + Behavioral Migraine Management	Propranolol HCL/nadolol	55 [53]	32.9 [5.8]	35.1 [6.7]	-2.2 (-4.6 to 0.2)	-0.4 (-0.7 to 0.0)
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**31.6 [6.9]**	**35.1 [6.7]**	**-3.5 (-5.9 to -1.1)**	**-0.5 (-0.9 to -0.1)**
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	32.9 [5.8]	31.6 [6.9]	1.3 (-0.9 to 3.5)	0.2 (-0.2 to 0.6)
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**63.4 [6.8]**	**57.7 [8.9]**	**5.7 (2.7 to 8.7)**	**0.7 (0.3 to 1.1)**

Appendix Table 163. Headache Specific Locus of Control at month 16 beta-blockers combined with behavioral therapy (orientation + relaxation training; migraine warning signs and triggers; effectively using migraine medication, and reducing impact of migraines; stress management or biofeedback training; migraine management plan) vs. beta-blockers alone for migraine prevention in adults, results from individual moderate risk of bias randomized controlled clinical trial[190] (continued)

Outcome	Active	Control	Randomized for active [control] treatment	Mean [standard deviation] with active treatment	Mean [standard deviation] with control treatment	Mean difference (95% CI)	Standardized mean difference (95% CI)
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**63.9 [7.7]**	**57.7 [8.9]**	**6.2 (3.2 to 9.2)**	**0.8 (0.4 to 1.1)**
Mean Internal Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	63.4 [6.8]	63.9 [7.7]	-0.5 (-3.1 to 2.1)	-0.1 (-0.4 to 0.3)
Mean HSE (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**143.4 [20.0]**	**127.5 [21.9]**	**15.9 (8.0 to 23.8)**	**0.8 (0.4 to 1.1)**
Mean HSE (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**144.8 [23.6]**	**127.5 [21.9]**	**17.3 (9.2 to 25.4)**	**0.8 (0.4 to 1.1)**
Mean HSE (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	143.4 [20.0]	144.8 [23.6]	-1.4 (-9.1 to 6.3)	-0.1 (-0.4 to 0.3)

Bold – significant at 95% confidence limit
CI – confidence interval

Appendix Table D164. Strength of evidence of comparative safety of beta-blockers for migraine prevention in adults (treatment discontinuation due to bothersome adverse effects in randomized controlled clinical trials)

Definition of the outcome	Reference	Active drug	Control drug	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Withdrew because of side effects and/or lack of efficacy	Louis, 1985[181]	Metoprolol	Clonidine	Moderate	Yes	NA	No	Low
Discontinued due to side-effects	Worz, 1991[184]	Metoprolol	Bisoprolol	Moderate	Yes	NA	No	Low
Patient withdrawal due to events	Schellenberg, 2008[187]	Metoprolol	Nebivolol	Moderate	Yes	NA	No	Low
Drowsiness leading to withdrawal	Grotemeyer, 1990[183]	Metoprolol	Acetylsalicylic acid	Moderate	Yes	NA	No	Low
Gastrointestinal side-effects leading to withdrawal	Grotemeyer, 1990[183]	Metoprolol	Acetylsalicylic acid	Moderate	Yes	NA	No	Low
Discontinued treatment because of severe adverse reactions	Langohr, 1985[182]	Clomipramine	Metoprolol	Moderate	Yes	NA	No	Low

NA – not applicable

Appendix Table D165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Insomnia	**Langohr, 1985[182] Moderate**	**Clomipramine 100mg/day**	**Metoprolol 100mg/day**	**15/63 [23.8]**	**2/63 [3.2]**	**7.5 (1.8 to 31.4)**	**0.21 (0.09 to 0.32)**
Sweating	**Langohr, 1985[182] Moderate**	**Clomipramine 100mg/day**	**Metoprolol 100mg/day**	**9/63 [14.3]**	**1/63 [1.6]**	**9.0 (1.2 to 69.0)**	**0.13 (0.04 to 0.22)**
Tiredness	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	7/63 [11.1]	9/63 [14.3]	0.8 (0.3 to 2.0)	-0.03 (-0.15 to 0.08)
Constipation	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	6/63 [9.5]	1/63 [1.6]	6.0 (0.7 to 48.4)	0.08 (0.00 to 0.16)
Nausea	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	5/63 [7.9]	2/63 [3.2]	2.5 (0.5 to 12.4)	0.05 (-0.03 to 0.13)
Dizziness	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	4/63 [6.3]	1/63 [1.6]	4.0 (0.5 to 34.8)	0.05 (-0.02 to 0.12)
Loss of appetite	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	3/63 [4.8]	1/63 [1.6]	3.0 (0.3 to 28.1)	0.03 (-0.03 to 0.09)
Restlessness	Langohr, 1985[182] Moderate	Clomipramine 100mg/day	Metoprolol 100mg/day	2/63 [3.2]	2/63 [3.2]	1.0 (0.1 to 6.9)	0.00 (-0.06 to 0.06)
Adverse events	Worz, 1991[184] Moderate	Metoprolol 50 to 100mg twice daily	Bisoprolol 5 to 10mg once daily	18/78 [23.1]	23/78 [29.5]	0.8 (0.5 to 1.3)	-0.06 (-0.20 to 0.07)
Dizziness	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	4/125 [3.2]	8/125 [6.4]	0.5 (0.2 to 1.6)	-0.03 (-0.08 to 0.02)
Tiredness/fatigue	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	7/125 [5.6]	3/125 [2.4]	2.3 (0.6 to 8.8)	0.03 (-0.02 to 0.08)
Sleep disturbances	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	6/125 [4.8]	2/125 [1.6]	3.0 (0.6 to 14.6)	0.03 (-0.01 to 0.08)
Cardiovascular, hypotensive reactions	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	1/125 [0.8]	6/125 [4.8]	0.2 (0.0 to 1.4)	-0.04 (-0.08 to 0.00)

Appendix Table 165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Gastrointestinal disturbances	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	2/125 [1.6]	5/125 [4.0]	0.4 (0.1 to 2.0)	-0.02 (-0.06 to 0.02)
Adverse effects	Worz, 1992[185] Moderate	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	19/125 [15.2]	23/125 [18.4]	0.8 (0.5 to 1.4)	-0.03 (-0.12 to 0.06)
Patients with treatment-related events	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	13/14 [92.9]	11/16 [68.8]	1.4 (0.9 to 1.9)	0.24 (-0.02 to 0.51)
Patients reporting mild events	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	1/14 [7.1]	4/16 [25.0]	0.3 (0.0 to 2.3)	-0.18 (-0.43 to 0.07)
Patients reporting moderate events	**Schellenberg, 2008[187] Moderate**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**12/14 [85.7]**	**6/16 [37.5]**	**2.3 (1.2 to 4.5)**	**0.48 (0.18 to 0.78)**
Patients reporting severe events	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	6/14 [42.9]	2/16 [12.5]	3.4 (0.8 to 14.3)	0.30 (0.00 to 0.61)
Fatigue	**Schellenberg, 2008[187] Moderate**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**11/14 [78.6]**	**7/16 [43.8]**	**1.8 (1.0 to 3.3)**	**0.35 (0.02 to 0.67)**
Bradycardia	**Schellenberg, 2008[187] Moderate**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**5/14 [35.7]**	**1/16 [6.3]**	**5.7 (0.8 to 43.2)**	**0.29 (0.02 to 0.57)**

Appendix Table 165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Hypotension	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	1/16 [6.3]	2.3 (0.2 to 22.6)	0.08 (-0.14 to 0.30)
Supraventricular extrasystoles	Schellenberg, 2008[187] Moderate	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	0/16 [0.0]	5.7 (0.3 to 108.9)	0.14 (-0.06 to 0.35)
At least one AE	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	53/135 [39.3]	42/135 [31.1]	1.3 (0.9 to 1.8)	0.08 (-0.03 to 0.19)
Skin and appendices disorders	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 300mg/day**	**9/135 [6.7]**	**2/135 [1.5]**	**4.5 (1.0 to 20.4)**	**0.05 (0.01 to 0.10)**
Musculo-skeletal system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	2/135 [1.5]	0.5 (0.0 to 5.4)	-0.01 (-0.03 to 0.02)
Central & peripheral nervous system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	4/135 [3.0]	3/135 [2.2]	1.3 (0.3 to 5.8)	0.01 (-0.03 to 0.05)
Autonomic nervous system disorders	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week**	**Acetylsalicylic acid 300mg/day**	**11/135 [8.1]**	**0/135 [0.0]**	**23.0 (1.4 to 386.4)**	**0.08 (0.03 to 0.13)**

Appendix Table 165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
		and 200mg/day thereafter)					
Vision disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Hearing and vestibular disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Psychiatric disorders	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 300mg/day**	**16/135 [11.9]**	**2/135 [1.5]**	**8.0 (1.9 to 34.1)**	**0.10 (0.05 to 0.16)**
Gastrointestinal system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	25/135 [18.5]	30/135 [22.2]	0.8 (0.5 to 1.3)	-0.04 (-0.13 to 0.06)
Liver and biliary system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	1/135 [0.7]	1.0 (0.1 to 15.8)	0.00 (-0.02 to 0.02)
Endocrine disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	0/135 [0.0]	1/135 [0.7]	0.3 (0.0 to 8.1)	-0.01 (-0.03 to 0.01)

Appendix Table 165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Cardiovascular disorders, general	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Vascular (extracardiac) disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	5/135 [3.7]	0/135 [0.0]	11.0 (0.6 to 197.0)	0.04 (0.00 to 0.07)
Respiratory system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	6/135 [4.4]	1/135 [0.7]	6.0 (0.7 to 49.2)	0.04 (0.00 to 0.07)
White blood cell disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	2/135 [1.5]	0/135 [0.0]	5.0 (0.2 to 103.2)	0.01 (-0.01 to 0.04)
Urinary system disorders	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	2/135 [1.5]	4/135 [3.0]	0.5 (0.1 to 2.7)	-0.01 (-0.05 to 0.02)
Reproductive disorders, female	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	2/135 [1.5]	1/135 [0.7]	2.0 (0.2 to 21.8)	0.01 (-0.02 to 0.03)
Body as a whole general disorders	**Diener, 2001[186] Low**	**Metoprolol 200mg/day**	**Acetylsalicylic acid**	**11/135 [8.1]**	**3/135 [2.2]**	**3.7 (1.0 to 12.9)**	**0.06 (0.01 to 0.11)**

Appendix Table 165. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse effect	Reference Risk of bias	Active drug Dose	Control drug Dose	Events/ randomized [rate of outcome in active group, %]	Events/ randomized [rate of outcome in control group, %]	Relative risk (95% CI)	Absolute risk difference (95% CI)
		(100mg/day in the first week and 200mg/day thereafter)	**300mg/day**				
Non-medical	Diener, 2001[186] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Acetylsalicylic acid 300mg/day	1/135 [0.7]	1/135 [0.7]	1.0 (0.1 to 15.8)	0.00 (-0.02 to 0.02)
Total adverse effects	**Diener, 2001[186] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Acetylsalicylic acid 300mg/day**	**99/135 [73.3]**	**51/135 [37.8]**	**1.9 (1.5 to 2.5)**	**0.36 (0.24 to 0.47)**

Bold - significant differences at 95% confidence limit
CI – confidence interval

Appendix Table D166. Strength of evidence about treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial[188]

Definition of the outcome	Active treatment	Control treatment	Risk of bias	Directness	Consistency	Precision	Strength of evidence
Withdrawn due to side-effects	Spinal Manipulation	Amitriptyline	Moderate	Yes	NA	No	Low
Withdrawn due to side-effects	Spinal Manipulation + Amitriptyline	Amitriptyline	Moderate	Yes	NA	No	Low
Withdrawn due to side-effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline	Moderate	Yes	NA	No	Low

Appendix Table D167. Treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial[188]

Outcome	Active treatment	Control treatment	Events/randomized rate, % with active treatment	Events/randomized rate, % with control treatment	Relative risk (95% CI)	Absolute risk difference (95% CI)
Withdrawn due to side-effects	**Spinal Manipulation The spinal manipulation administered was a type described as high-velocity, low-amplitude, and short-lever arm.**	**Amitriptyline 100mg/day**	**0/7 0.05**	**7/77 10.05**	**0.1 (0.0 to 1.0)**	**-0.10 (-0.17 to -0.03)**
Withdrawn due to side-effects	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/day	4/7 5.65	7/71 10.05	0.6 (0.2 to 1.8)	-0.04 (-0.13 to 0.04)
Withdrawn due to side-effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	0/4 0.05	4/77 5.65	0.1 (0.0 to 1.9)	-0.06 (-0.11 to 0.00)
Withdrawn	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	17/15 23.95	15/71 21.45	1.1 (0.6 to 2.1)	0.03 (-0.11 to 0.16)
Withdrawn	Spinal Manipulation	Amitriptyline 100mg/day	19/15 24.75	15/77 21.45	1.2 (0.6 to 2.1)	0.03 (-0.10 to 0.17)
Withdrawn	Spinal Manipulation	Amitriptyline + Spinal Manipulation	19/17 24.75	17/77 23.95	1.0 (0.6 to 1.8)	0.01 (-0.13 to 0.15)

Bold - significant at 95% confidence limit
CI – confidence interval

Table D168. Net-work Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials

Control / Active	Placebo	Topiramate	Valproate	Propranolol	Divalproex	Flunarizine	Off label beta-blockers	Anti-depressants	Off label anti-epileptics	Other off label drugs
Topiramate	**2.2 (1.5;3.4)**		1.1 (0.2;7.3)	1.5 (0.6;3.9)	0.5 (0.1;2.4)	1.3 (0.5;3.7)	**4.5 (1.8;11.5)**	0.9 (0.5;1.5)	1.2 (0.6;2.5)	0.6 (0.2;1.3)
Valproate	2.0 (0.3;12.8)	1.0 (0.1;6.0)		1.4 (0.2;9.7)	0.5 (0.0;4.8)	1.2(0.2;8.5)	4.0 (0.6;35.7)	0.8 (0.1;5.3)	1.1 (0.2;8.0)	0.5 (0.1;2.9)
Propranolol	1.5 (0.6;3.5)	0.7 (0.3;1.7)	0.7 (0.1;5.1)		0.4 (0.1;1.5)	0.9(0.4;1.8)	**3.0 (1.1;8.5)**	0.6 (0.2;1.5)	0.8 (0.3;2.3)	**0.4 (0.1;0.9)**
Divalproex	**4.2 (1.0;21.7)**	1.9 (0.4;10.4)	2.0 (0.2;24.6)	2.8 (0.7;15.3)		2.5 (0.5;14.2)	**8.5 (1.7;52.3)**	1.6 (0.4;8.9)	2.2 (0.5;12.9)	1.1 (0.2;6.0)
Flunarizine	1.7 (0.6;4.6)	0.8 (0.3;2.2)	0.8 (0.1;5.9)	1.2 (0.6;2.4)	0.4 (0.1;2.1)		**3.4 (1.3;10.3)**	0.7 (0.2;1.9)	0.9 (0.3;2.9)	0.4 (0.2;1.1)
Off label beta-blockers	0.5 (0.2;1.1)	0.2 (0.1;0.6)	0.2 (0.0;1.8)	**0.3 (0.1;0.9)**	**0.1 (0.0;0.6)**	**0.3 (0.1;0.8)**		**0.2 (0.1;0.5)**	**0.3 (0.1;0.7)**	**0.1 (0.0;0.3)**
Antidepressants	**2.5 (1.5;4.5)**	1.2 (0.6;2.1)	1.2 (0.2;8.2)	1.8 (0.7;4.4)	0.6 (0.1;2.8)	1.5 (0.5;4.2)	**5.2 (2.1;13.1)**		1.4 (0.6;3.1)	0.6 (0.3;1.5)
Off label anti epileptics	**1.8 (1.0;3.4)**	0.8 (0.4;1.6)	0.9 (0.1;6.3)	1.3 (0.4;3.6)	0.4 (0.1;2.1)	1.1 (0.3;3.3)	**3.7 (1.4;10.2)**	0.7 (0.3;1.6)		0.5 (0.2;1.2)
Other off label drugs	**3.9 (1.8;9.5)**	1.8 (0.7;4.6)	1.9 (0.3;12.2)	**2.8 (1.1;7.1)**	0.9 (0.2;4.7)	2.4 (0.9;6.2)	**8.1 (2.9;26.2)**	1.6 (0.7;3.9)	2.2 (0.8;6.3)	

Appendix Table D169. Decrease in frequency of migraine >50% with amitriptyline vs. placebo in adults with different baseline migraine frequency, results from moderate risk of bias RCT[108]

Baseline migraine frequency	Weeks of treatment	Relative risk (95% CI)	Absolute risk difference (95% CI)
Baseline ≥17 Headaches per month	4	5.5 (0.7 to 40.5)	**0.20 (0.04 to 0.37)**
Baseline 1-16 Headaches per month	4	0.7 (0.3 to 1.5)	-0.04 (-0.10 to 0.03)
Baseline ≥17 Headaches per month	8	1.7 (0.5 to 5.4)	0.14 (-0.12 to 0.39)
Baseline 1-16 Headaches per month	8	1.0 (0.5 to 2.2)	0.00 (-0.08 to 0.08)
Baseline ≥17 Headaches per month	12	5.0 (0.7 to 34.3)	**0.37 (0.11 to 0.63)**
Baseline 1-16 Headaches per month	12	1.2 (0.6 to 2.5)	0.02 (-0.08 to 0.12)
Baseline ≥17 Headaches per month	16	1.8 (0.5 to 7.1)	0.16 (-0.16 to 0.48)
Baseline 1-16 Headaches per month	16	0.8 (0.4 to 1.8)	-0.03 (-0.13 to 0.07)

Bold – significant difference at 95% confidence limit
CI – confidence interval

Appendix Table D170. Improvement of M score >50%* with amitriptyline vs. placebo in adults with different baseline M score and depressive symptoms, results from moderate risk of bias RCT[100]

Baseline condition	Relative risk (95% CI)	Absolute risk difference (95% CI)
Baseline H<14	1.6 (1.0 to 2.5)	0.21 (0.00 to 0.43)
Baseline H>=14	1.5 (0.4 to 5.7)	0.13 (-0.29 to 0.54)
Baseline M<100	1.7 (0.9 to 3.0)	0.21 (-0.01 to 0.43)
Baseline M<100 AND H<14	1.5 (0.8 to 2.8)	0.16 (-0.08 to 0.40)
Baseline M<100 AND H>14	3.0 (0.8 to 11.3)	0.50 (-0.02 to 1.02)
Baseline M≥100	1.4 (0.7 to 2.9)	0.21 (-0.18 to 0.59)
Baseline M≥100 AND H<14	**1.7 (1.0 to 3.1)**	**0.44 (0.10 to 0.79)**
Baseline M≥100 AND H>14	0.3 (0.0 to 6.4)	-0.25 (-0.73 to 0.23)

M score = 2 (frequency*duration) Disabling+1 (frequency*duration) Severe; H SCORE=Hamilton Physician Depression Rating Scale (0-7 normal, 20 - severe depression)
Bold – significant difference at 95% confidence limit
CI – confidence interval

Appendix Table D171. Prediction of ≥50% in migraine days reduction per month with different doses of amitriptyline (50 vs. 25mg/day) for migraine prevention in adults, results from moderate risk of bias RCT[107]

Predictor of effect	Odds ratio (95% CI)
Age (+1 year)	1.08 (0.99 to 1.17)
Age at onset of migraine (+1 year)	1.04 (0.94 to 1.16)
Amitriptyline ER 50 mg per day (versus not)	0.24 (0.06 to 1.04)
Duration of attack (+1 h)	1.04 (0.98 to 1.12)
Male gender (versus female)	2.1 (0.45 to 9.87)
Migraine days per month (+1 day)	**2.35 (1.45 to 3.8)**
Migraine with aura (versus not)	0.63 (0.13 to 3.12)
Number of drugs (+1 drug)	1.02 (0.67 to 1.55)
Pain intensity per attack (+1 score point)	0.69 (0.46 to 1.04)
Positive family history of migraine (versus negative)	2.35 (0.57 to 9.72)
Smoker (versus not)	2.23 (0.44 to 11.3)

Bold – significant difference at 95% confidence limit
CI – confidence interval

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Preventive Pharmacological Treatments for Migraine in Children

Appendixes

Appendix A. Literature Search
Appendix B. Ongoing Studies
Appendix C. Analytical Framework
Appendix D. Evidence Tables
Appendix E. Excluded Studies

Appendix A. Literature Search

January 2011
PubMed

#	Strings	N
#8	Search **"Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh]** Limits: **Humans, Meta-Analysis, English**	97
#7	Search **"Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh]** Limits: **Humans, Randomized Controlled Trial, English**	907

#	Strings	N
#71	Search **migraine NOT acute** Limits: **Humans, Randomized Controlled Trial, English**	655
#70	Search **migraine** Limits: **Humans, Randomized Controlled Trial, English**	1040
#66	Search **melatonin AND migraine**	55
#67	Search **melatonin AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	7
#64	Search **"Brain-Derived Neurotrophic Factor"[Mesh] AND migraine**	6
#63	Search **"Brain-Derived Neurotrophic Factor"[Mesh] AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	1
#62	Search **"Brain-Derived Neurotrophic Factor"[Mesh]** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	94
#58	Search **Risperidone AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#57	Search **Paliperidone AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#56	Search **Methiothepin AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#55	Search **Metergoline AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#53	Search **Lisuride AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	5
#51	Search **Bromocriptine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	4
#50	Search **Zotepine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#49	Search **Ziprasidone AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#48	Search **Trifluoperazine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#47	Search **Tenilapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#46	Search **Sulpiride AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	1
#45	Search **Spiperone AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#44	Search **Sertindole AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#43	Search **Olanzapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#42	Search **Loxapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#41	Search **Ketanserin AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#40	Search **Imipramine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#39	Search **Fluperlapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0

#38	Search **Fluphenazine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#36	Search **Cyproheptadine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	9
#35	Search **Clozapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#33	Search **Clomipramine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	2
#32	Search **Aripiprazole AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#31	Search **Amoxapine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#29	Search **Amitriptyline AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	34
#28	Search **Amitriptyline AND migraine** Limits: **Humans, English**	150
#27	Search **5-HT7 AND migraine** Limits: **Humans, English**	12
#24	Search **5-HT7** Limits: **Humans, English**	150
#13	Search **Quetiapine AND migraine** Limits: **Humans, English**	5
#21	Search **"Antipsychotic Agents "[Pharmacological Action] AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	41
#20	Search **"Antipsychotic Agents "[Pharmacological Action] AND migraine** Limits: **Humans, English**	206
#19	Search **"Antipsychotic Agents "[Pharmacological Action]** Limits: **Humans, English**	51308
#11	Search **5-HT2A AND migraine** Limits: **Humans, English**	14
#10	Search **5-HT2A antagonists AND migraine** Limits: **Humans, English**	3
#7	Search **5-HT2A antagonists** Limits: **Humans, English**	394
#5	Search **Alpha-2 agonists AND migraine** Limits: **Humans, English**	6
#4	Search **Alpha-2 agonists AND migraine**	17

#84	Search **telcagepant AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	4
#83	Search **olcegepant AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#82	Search **Arachidonic cascade modulators** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#80	Search **tonabersat) AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	6
#79	Search **dextromethorphan AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#78	Search **dextromethorphan AND migraine NOT acute** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#77	Search **loxapine AND migraine NOT acute** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	0
#76	Search **prochlorperazine AND migraine NOT acute** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	8
#75	Search **prochlorperazine AND migraine** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English**	20

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#	Strings	N
#15	Search **Phenelzine AND migraine** Limits: **Humans, Journal Article, English**	11
#14	Search **Bupropion AND migraine** Limits: **Humans, Journal Article, English**	1
#13	Search **Imipramine AND migraine** Limits: **Humans, Journal Article, English**	15
#12	Search **Imipramine AND headache** Limits: **Humans, Journal Article, English**	60
#11	Search **Doxepin AND headache** Limits: **Humans, Journal Article, English**	15
#9	Search **Desipramine AND headache** Limits: **Humans, Journal Article, English**	13
#10	Search **Desipramine AND migraine** Limits: **Humans, Journal Article, English**	1
#7	Search **Protriptyline AND headache** Limits: **Humans, Journal Article, English**	4
#6	Search **Protriptyline AND migraine** Limits: **Humans, Journal Article, English**	0

Updated search in Ovid; 1948 to November Week 3 2011

#	Searches	Results
1	exp migraine disorders/dt	5944
2	exp migraine disorders/pc	1669
3	ad.fs.	998247
4	2 and 3	286
5	1 or 4	6112
6	1 or 2	7065
7	exp "off-label use"/	519
8	off label.mp.	2412
9	7 or 8	2412
10	6 and 9	14
11	exp calcium channel blockers/	68976
12	exp antihypertensive agents/	216956
13	exp antidepressive agents/	113058
14	exp anticonvulsants/	111349
15	exp botulinum toxin type a/	4832
16	exp alzheimer disease/dt	8107
17	11 or 12 or 13 or 14 or 15 or 16	476372
18	6 and 17	1675
19	5 or 10 or 18	6489
20	limit 19 to (humans and yr="2000 -Current")	3195
21	limit 20 to updaterange="mesz(20111121020154-20111121091315]"	0

Search for systematic reviews:

Searches	Results
Search systematic[sb] AND (quetiapine) AND child	16
Search systematic[sb] AND (Telmisartan) AND child	1
Search systematic[sb] AND (Captopril) AND child	5
Search systematic[sb] AND (Enalapril) AND child	2
Search systematic[sb] AND (Femoxetine) AND child	0
Search systematic[sb] AND (Metoprolol) AND child	4
Search systematic[sb] AND (acebutolol) AND child	0
Search systematic[sb] AND (bisoprolol) AND child	0
Search systematic[sb] AND (Atenolol) AND child	2
Search systematic[sb] AND (opipramol) AND child	0
Search systematic[sb] AND (Nadolol) AND child	0
Search systematic[sb] AND (Oxprenolol) AND child	0
Search systematic[sb] AND (Alprenolol) AND child	0
Search systematic[sb] AND (Labetalol) AND child	1
Search systematic[sb] AND (Timolol) AND child	2
Search systematic[sb] AND (Propranolol) AND child	17
Search systematic[sb] AND (Pindolol) AND child	0
Search systematic[sb] AND (Pindolol)	18
Search systematic[sb] AND (Rizatriptan) AND child	6
Search systematic[sb] AND (Zolmitriptan) AND child	5
Search systematic[sb] AND (Frovatriptan) AND child	0
Search systematic[sb] AND (Almotriptan) AND child	1
Search systematic[sb] AND (Sumatriptan) AND child	13
Search systematic[sb] AND (Venlafaxine) AND child	8
Search systematic[sb] AND (Paroxetine) AND child	13
Search systematic[sb] AND (citalopram) AND child	12
Search systematic[sb] AND (fluvoxamine) AND child	12
Search systematic[sb] AND (Nicardipine) AND child	1
Search systematic[sb] AND (Verapamil) AND child	4
Search systematic[sb] AND (Nimodipine) AND child	5
Search systematic[sb] AND (Nifedipine) AND child	4
Search systematic[sb] AND (Telcagepant) AND child	0
Search systematic[sb] AND (Olanzapine) AND child	18

Search systematic[sb] AND (aripiprazole) AND child	16
Search systematic[sb] AND (Pizotifen) AND child	9
Search systematic[sb] AND (Lasmiditan) AND child	0
Search systematic[sb] AND (Lasmiditan hydrochloride) AND child	0
Search systematic[sb] AND (Quinazoline) AND child	4
Search systematic[sb] AND (Piperazine) AND child	1
Search systematic[sb] AND (Clonidine) AND child	28
Search systematic[sb] AND (nortriptyline) AND child	4
Search systematic[sb] AND (mirtazapine) AND child	2
Search systematic[sb] AND (Memantine) AND child	3
Search systematic[sb] AND (Amantadine) AND child	27
Search systematic[sb] AND (Botulinum Toxin Type A) AND child	35
Search systematic[sb] AND (Montelukast) AND child	19
Search systematic[sb] AND (Simvastatin) AND child	5
Search systematic[sb] AND (cimetidine) AND child	2
Search systematic[sb] AND (Indomethacin) AND child	10
Search systematic[sb] AND (Flurbiprofen) AND child	0
Search systematic[sb] AND (Valproic acid) AND child	36
Search systematic[sb] AND (Divalproex) AND child	40
Search systematic[sb] AND (Topiramate) AND child	24
Search systematic[sb] AND (Eletriptan) AND child	1
Search systematic[sb] AND (Naratriptan) AND child	0
Search systematic[sb] AND (Pregabalin) AND child AND adverse	1
Search systematic[sb] AND (Levetiracetam) AND child AND adverse	4
Search systematic[sb] AND (amitriptyline) AND child AND adverse	6
Search systematic[sb] AND (carbamazepine) AND child AND adverse	28
Search systematic[sb] AND (Prochlorperazine) AND child AND adverse	2
Search systematic[sb] AND (melatonin) AND child AND adverse	7
Search systematic[sb] AND (melatonin) AND child	16
Search systematic[sb] AND (Naproxen) AND child	6
Search systematic[sb] AND (flunarizine) AND child	5
Search systematic[sb] AND (Dihydroergocryptine) AND child	0
Search systematic[sb] AND (dihydroergotamine) AND child	5
Search systematic[sb] AND (Ergotamine) AND child	1

March 29, 2012

#	Searches	Results
1	exp migraine disorders/dt	5944
2	exp migraine disorders/pc	1674
3	ad.fs.	991506
4	2 and 3	288
5	1 or 4	6107
6	1 or 2	7059
7	exp "off-label use"/	571
8	off label.mp.	2478
9	7 or 8	2478
10	6 and 9	14
11	exp calcium channel blockers/	68415
12	exp antihypertensive agents/	215895
13	exp antidepressive agents/	112330
14	exp anticonvulsants/	111378
15	exp botulinum toxin type a/	4780
16	exp alzheimer disease/dt	8048
17	11 or 12 or 13 or 14 or 15 or 16	474031
18	6 and 17	1675
19	5 or 10 or 18	6481
20	limit 19 to (humans and yr="2000 -Current")	3194
21	limit 20 to updaterange="mesz(20111121020154-20111121091315]"	0

Appendix B. Ongoing Studies of Migraine Prevention in Children

NCT ID	Interventions	Sponsors	Phases	Enrollment	Study Designs
NCT00269581	Other: Educational CD-rom|Other: Headstrong CD-rom	University of Kansas|National Institute of Neurological Disorders and Stroke (NINDS)	Phase III	92	Allocation: Randomized|Control: Active Control|Endpoint Classification: Efficacy Study|Intervention Model: Parallel Assignment|Masking: Open Label|Primary Purpose: Treatment
NCT00665236	Other: Craniosacral therapy|Procedure: Low strength static magnets	University of North Carolina, Chapel Hill|National Center for Complementary and Alternative Medicine (NCCAM)		66	Allocation: Randomized|Control: Placebo Control|Endpoint Classification: Efficacy Study|Intervention Model: Parallel Assignment|Masking: Single Blind (Outcomes Assessor)|Primary Purpose: Treatment
NCT00237302	Drug: topiramate	Ortho-McNeil Neurologics, Inc.	Phase III	162	Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Prevention
NCT00210535	Drug: Topiramate; Placebo	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	Phase III	110	Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Treatment
NCT00195806	Drug: divalproex sodium	Abbott	Phase III	315	Allocation: Non-Randomized|Control: Uncontrolled|Endpoint Classification: Safety Study|Intervention Model: Single Group Assignment|Masking: Open Label|Primary Purpose: Treatment
NCT00195741	Drug: divalproex sodium	Abbott	Phase III	300	Allocation: Randomized|Control: Placebo Control|Endpoint Classification: Safety Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Treatment
NCT00195754	Drug: divalproex sodium	Abbott	Phase III	114	Allocation: Non-Randomized|Control: Uncontrolled|Endpoint Classification: Safety Study|Intervention Model: Single Group Assignment|Masking: Open Label|Primary Purpose: Treatment
NCT00231595	Drug: topiramate	Johnson & Johnson Pharmaceutical	Phase III	480	Allocation: Randomized|Control: Placebo Control|Endpoint Classification: Safety/Efficacy

NCT ID	Interventions	Sponsors	Phases	Enrollment	Study Designs
		Research & Development, L.L.C.			Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Treatment
NCT00236561	Drug: topiramate, propranolol	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	Phase III	568	Allocation: Randomized|Control: Placebo Control|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Treatment
NCT00236509	Drug: topiramate	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	Phase III	480	Allocation: Randomized|Control: Placebo Control|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Treatment
NCT00158002	Drug: Topiramate	Monarch Medical Research|Ortho-McNeil Neurologics, Inc.	Phase II	40	Allocation: Non-Randomized|Control: Uncontrolled|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Masking: Open Label|Primary Purpose: Educational/Counseling/Training
NCT00131443	Drug: Topiramate	Monarch Medical Research|Ortho-McNeil Neurologics, Inc.	Phase II|Phase III	40	Allocation: Randomized|Control: Dose Comparison|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Masking: Double-Blind|Primary Purpose: Educational/Counseling/Training
NCT01035983	Drug: Frovatriptan 2.5 mg	Endo Pharmaceuticals|Vernalis (R&D) Ltd	Phase III	550	Endpoint Classification: Safety Study|Intervention Model: Single Group Assignment|Masking: Open Label|Primary Purpose: Treatment
NCT00475514	Drug: Frovatriptan 2.5mg QD|Drug: Frovatriptan 2.5 mg BID|Drug: placebo	Endo Pharmaceuticals	Phase III		Allocation: Randomized|Control: Placebo Control|Intervention Model: Parallel Assignment|Masking: Double-Blind
NCT00203255	Drug: Soy Isoflavones	Thomas Jefferson University|Johnson & Johnson		25	Allocation: Non-Randomized|Control: Uncontrolled|Endpoint Classification: Efficacy Study|Intervention Model: Single Group Assignment|Masking: Open Label
NCT00551980	Behavioral: Cognitive, Relaxation, Exercise Therapy	University of Turin, Italy|Compagnia di San Paolo|Comune di Torino|CPO Piemonte|Regione Piemonte	Phase III	2895	Allocation: Randomized|Control: Active Control|Endpoint Classification: Efficacy Study|Intervention Model: Parallel Assignment|Masking: Open Label|Primary Purpose: Treatment

Appendix C. Analytical Framework

PICOTS Framework

Population(s)

Children with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society[1] (see below for definitions).

Patient characteristics that can modify the effects of pharmacological treatments for preventing migraine attacks in children and adults:

- Age
- Sex
- The onset of menarche
- Race and ethnicity
- Socioeconomic status
- Education
- Family history
- Access to care, type of care, and residence in rural or urban areas
- Definition of migraine
- Presence of aura
- Headache frequency
- Prior treatments; overuse of drugs for acute migraine
- Obesity
- Nutritional and dietary factors, specifically caffeine
- Aerobic fitness
- Previous head injury
- Psychological factors and social/family support system
- Comorbidities (depression, bipolar disorder, anxiety, diabetes, hypertension, cardiovascular diseases, others)
- Concomitant medications for comorbid conditions

Interventions

Off-label medications previously examined in clinical trials for preventing migraine.[2]

Monotherapy.

Multidrug interventions.

Combined pharmacological with nonpharmacological modalities: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Comparators

Placebo.

Drug treatments (comparative effectiveness).

Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Outcomes

Patient-centered outcomes:

- Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review.
- Quality of life.
- Patient satisfaction.
- Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes.
- Emergency visits, loss of school days; treatment failure.

Intermediate outcomes:

- Number of headache days.
- Number of moderate to severe headache days.
- Improvement in associated symptoms.
- Use of drugs for acute migraine (prescribed or over-counter).
- Physician/healthcare professional (HCP) visits.

Harms:

- All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness).
- Treatment discontinuation due to adverse effects.
- Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).

Timing

6 months or more; optimally 12 months

Any time of occurrence for the harms

Setting

Outpatient settings

Definition of Terms

Migraine (as defined by the Headache Classification Subcommittee of the International Headache Society):[1]

Repeated attacks of headache lasting 4 to 72 hours in patients with a normal physical examination, no other reasonable cause for the headache, and

At least two of the following features:

- Unilateral pain
- Throbbing pain
- Aggravation by movement
- Moderate or severe intensity

Plus at least one of the following features:

- Nausea/vomiting
- Photophobia and phonophobia

Episodic migraine as an indication for preventive treatment:

- Five or more attacks a month[3]
- Three or more attacks a month[3]

Definitions of chronic migraine (can be chronic from onset or transformed from episodic migraine):

FDA:

- Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.[4]

Revised International Headache Society criteria for chronic migraine:[1]

1.5.1. Chronic migraine

E. Headache (tension-type and/or migraine) on *≥15 days per month for at least 3 months*

* Characterization of a frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least 1 month.

F. Occurring in a patient who has had at least five attacks.

G. On ≥8 days per month for at least 3 months headache has fulfilled C.1 and/or C.2 below; that is, has fulfilled criteria for pain and associated symptoms of migraine without aura.

2. Has at least two of a–d
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe pain intensity
   d. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) and at least one of (1) or (2):
      (3). Nausea and/or vomiting
      (4). Photophobia and phonophobia
3. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above

H. No medication overuse† and not attributed to another causative disorder

†Headache Classification Committee criteria for a medication overuse headache (A8.2)[1]

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1. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID 16686915.
2. Rapoport A. Antimigraine drugs: new frontiers. Neurol Sci. 2009 May;30 Suppl 1:S49-54. PMID 19415426.
3. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
4. Administration USFaD. FDA News Release: FDA approves Botox to treat chronic migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.

Appendix Table C1. Pharmacological classes for migraine prevention

Drug, ATC Code*	Class of Drug
ANTIEPILEPTICS	
Topiramate, N03AX11	N03 ANTIEPILEPTICS N03AX Other antiepileptics
Lamotrigine, N03AX09	N03A ANTIEPILEPTICS
Levetiracetam, N03AX14	N03A ANTIEPILEPTICS
Pregabalin, N03AX16	N03A ANTIEPILEPTICS alpha2-delta agonist
Carbamazepine , N03AF01	N03A ANTIEPILEPTICS N03AF Carboxamide derivatives
Valproic acid, N03AG01	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, Gamma-aminobutyric acid (GABA) enhancer and analog
Vigabatrin, N03AG04	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, GABA transaminase inhibitor
Tiagabine, N03AG06	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, gamma aminobutyric acid (GABA) enhancer
Zonisamide, N03AX15	N03A ANTIEPILEPTICS N03AX Other antiepileptics
Valproate	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives
Divalproex	Gamma-aminobutyric acid (GABA) enhancer and analog
Gabapentin, N03AX12	N03A ANTIEPILEPTICS
Acetazolamide, S01EC01	S01EC, carbonic anhydrase inhibitor
ANTIDEPRESSANTS	
Nortriptyline , N06AA10	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Clomipramine, N06AA04	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Citalopram, N06AB04	N06A ANTIDEPRESSANTS N06AB Selective serotonin reuptake inhibitors
Venlafaxine, N06AX16	N06A ANTIDEPRESSANTS N06AX Other antidepressants
Amitriptyline	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Mirtazapine, N06AX11	N06A ANTIDEPRESSANTS tricyclic antidepressants
BETA BLOCKERS	
Timolol, C07AA06	C07AA , Beta blocking agents, nonselective
Nadolol , C07AA12	C07AA Beta blocking agents, nonselective
Propranolol,C07AA05	C07AA Beta blocking agents, nonselective
Metoprolol,C07AB02	C07AB Beta blocking agents, selective
Atenolol, C07AB03	C07AB Beta blocking agents, selective
Bisoprolol,C07AB07	C07AB Beta blocking agents, selective
Acebutolol,C07AB04	C07AB Beta blocking agents, selective
Alprenolol, C07AA01 Oxprenolol, C07AA02 (discontinued in the FDA)	C07A BETA BLOCKING AGENTS C07AA Beta blocking agents, nonselective
Pindolol, C07AA03	C07AA Beta blocking agents, nonselective
ACE INHIBITORS	
Trandolapril, C09AA10	C09AA ACE inhibitors
Enalapril,C09AA02	C09AA ACE inhibitors
Captopril,C09AA01	C09AA ACE inhibitors
Lisinopril, C09AA03	C09AA ACE inhibitors
ANGIOTENSIN II ANTAGONISTS	
Telmisartan,C09CA07	C09CA Angiotensin II antagonists
Candesartan, C09CA06	C09CA Angiotensin II antagonists
CALCIUM CHANNEL ANTAGONIST	
Dotarizine	SELECTIVE CALCIUM CHANNEL ANTAGONIST; 5-HT receptors ANTAGONIST
Flunarizine, N07CA03; Sibelium	SELECTIVE CALCIUM CHANNEL ANTAGONISTN07C ANTIVERTIGO PREPARATIONS

Appendix Table C1. Pharmacological classes for migraine prevention (continued)

Drug, ATC Code*	Class of Drug
SELECTIVE CALCIUM CHANNEL BLOCKERS	
Nimodipine,C08CA06	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Verapamil,C08DA01	C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS C08DA Phenylalkylamine derivatives
Nicardipine,C08CA04	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Nifedipine,C08CA05	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
ANTIADRENERGICS	
Clonidine,C02AC01	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
Labetalol, C07AG01	C07AG , Alpha and beta blocking agents
Dixarit (clonidine, C02AC01) Guanfacine, C02AC02	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
ANTI-DEMENTIA	
Donepezil, N06DA02 Memantine, N06DX01	N06 PSYCHOANALEPTICS N06D ANTI-DEMENTIA DRUGS N-methyl-D-aspartate (NMDA) receptor inhibitor
ANTIPSYCHOTICS	
Aripiprazole,N05AX12	N05A ANTIPSYCHOTICS
Olanzapine,N05AH03	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Quetiapine,N05AH04	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Deanxit (Flupentixol, N05AF01)	N05A ANTIPSYCHOTICS N05AF Thioxanthene derivatives
Sulpiride, N05AL01 (antipsychotic)	N05A ANTIPSYCHOTICS N05AL Benzamides
Prochlorperazine, N05AB04	N05A ANTIPSYCHOTICS
DOPAMINERGIC AGENTS	
Amantadine, N04BB01	N04B DOPAMINERGIC AGENTS N04BB Adamantane derivatives N-methyl-D-aspartate (NMDA) receptor inhibitor
Dihydroergocryptine, N04BC03	N04B DOPAMINERGIC AGENTS N04BC Dopamine agonists
ERGOT ALKALOIDS	
Dihydroergotamine, N02CA01	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Lisuride, N02CA07 Ergotamine, N02CA02	N02C ANTIMIGRAINE PREPARATIONS N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Methysergide, N02CA04	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
MUSCLE RELAXANTS	
Botulinum Toxin Type A, M03AX01	M03A MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS M03AX Other muscle relaxants, peripherally acting agents
Tizanidine, M03BX02	M03B MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
SYSTEMIC DRUGS	
Montelukast, R03DC03	R03D OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES R03DC Leukotriene receptor antagonists

ATC code - The Anatomical Therapeutic Chemical classification

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Appendix Table D1. Characteristics of children in 24 randomized controlled clinical trials about migraine prevention

Characteristics	Number of randomized trials that reported this information	Mean	Minimum	Maximum
Age	21	11.98	9.20	14.60
% females in sample	24	50.56	31.00	71.43
% Caucasian in sample	7	74.88	59.30	85.00
Duration of run in period in weeks	14	5.43	4.00	9.00
Headache frequency at baseline/month	17	8.33	3.20	17.30
Duration of migraine in years	9	3.49	2.20	4.70

Appendix Table D2. Reporting of characteristics of children in 24 randomized controlled clinical trials about migraine prevention

Characteristics	Factor distribution	Number of trials	% of total
Migraine definition	Ad Hoc Committee	2	8.7
Migraine definition	Classic migraine	1	4.35
Migraine definition	International Headache Society	14	60.87
Migraine definition	Not specified	3	13.04
Migraine definition	Vahlquist's criteria	3	13.04
% of patients without aura	Not reported	17	70.83
Exclusion criteria	Not reported	7	29.17
Duration of migraine	Not reported	14	58.33
% preventative treatment	Not reported	22	91.67
Concurrent medication	Not reported	12	50
Prior treatment	Not reported	23	95.83
Overuse of the drugs for acute migraine	Not reported	24	100
Family factors	Not reported	18	75
Health insurance status of subjects	Not reported	23	95.83
Hormone therapy	Not reported	24	100
Inclusion of pregnant women/birth control	Not reported	21	87.5
Menses	Not reported	24	100
Obesity	Not reported	20	83.33
Socio-economic condition, education	Not reported	24	100
Subject compliance and suitability	Not reported	16	66.67
Definition of adherence to treatments	Not reported	18	75
Adherence of subjects to assigned treatment	68% of the patients were ≥70% compliant with taking their study drug throughout the study	1	100

Appendix Table D3. Subject flow in 24 randomized controlled clinical trials about migraine prevention in children

Subject flow	Number randomized trials that reported this information	Mean	Minimum	Maximum
Number of screened potential subjects	3	339	46	504
Number of eligible subjects	5	113	37	192
Number of enrolled subjects	9	122	15	436
Total sample randomized to treatment	23	88	14	305
% analyzed	18	95.02	73.58	100.00
Number needed to screen	3	2	1	4
Total length of followup	24	20.13	6.00	52.00
Loss of followup in control group	7	9.40	3.33	24.68
Loss of followup in active group	8	8.06	3.33	16.98

Appendix Table D4. Risk of bias in 24 randomized controlled clinical trials about migraine prevention

Risk of bias criteria	Distribution of criteria	Number of trials	% of total
Risk of bias	Low	12	50
Risk of bias	Moderate	6	25
Risk of bias	Unclear	6	25
Masking of the treatment status	Double-blind	17	70.83
Masking of the treatment status	Not reported	6	25
Masking of the treatment status	Open-label	1	4.17
Intention to treat analysis preplanned	No	1	4.17
Intention to treat analysis preplanned	Not reported	11	45.83
Intention to treat analysis preplanned	Unclear	1	4.17
Intention to treat analysis preplanned	Yes	11	45.83
Allocation concealment	Adequate	5	20.8
Allocation concealment	Not adequate	1	4.17
Allocation concealment	Not reported	18	75

Appendix Table D5. Risk of bias by journal of the publication and funding of 24 randomized controlled clinical trials about migraine prevention

Distribution factor	Low risk of bias	Moderate risk of bias	Unclear risk of bias	Total	% of trials with low risk of bias
Total	12	6	6	24	50
Acta Neurol. Scandinav	1	0	0	1	100
Behaviour Research and Therapy	0	0	3	3	0
Cephalalgia	2	0	0	2	100
Development Medicine & Child Neurology	0	1	0	1	0
European Journal of Paediatric Neurology	0	0	1	1	0
Food and Drug Administration	1	0	0	1	100
Headache	6	4	0	10	60
Journal of Child Neurology	0	0	1	1	0
Pediatric Drugs	0	1	0	1	0
Pediatric Neurology	1	0	0	1	100
Pediatrics	1	0	1	2	50
Funding from Grant	1	1	3	5	20.0
Funding from Grant and Industry	0	1	0	1	0.0
Funding from Industry	4	2	0	6	66.7
No funding	0	1	1	2	0.0
Not reported	7	1	1	9	77.8
Other	0	0	1	1	0.0

Appendix Table D6. Randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine

Reference Design Sample Number analyzed % females	Age	Definition of migraine	Presence of aura	Baseline status	Overuse of drugs for acute migraine	Duration of migraine	Prior treatment	Subject compliance and suitability
Ludvigsson, 1974[1] Design RCT Sample 32 Number analyzed 28 43.75% female	Eligible age 7 to16 years Mean age Not reported	Ad hoc Committee on classification of headache 1962, Classification of headache, J.Amer.med. Ass., Bille 1962	4/32 had visual aura	Mean 3.4 attacks of headache per month	Not reported	4 years	Not reported	Not reported
Sillanpää, 1977[2] Design RCT Sample 57 Number analyzed 57 38.6% female	Eligible age 0-15 years Mean 11 years	Migraine was defined by the criteria of Vahlquist, i.e. paroxysmal headache separated by headache-free intervals and at least two of the following four: unilateral pain, nausea, visual aura and positive family history.	12 patients in the clonidine group and 8 patients in the placebo group had classic migraine with visual aura.	Frequency of headache/month(n): 1-2: Clonidine: 8, Placebo: 7, 3-4: Clonidine: 12 and Placebo: 12 , 5-6: Clonidine: 3 and Placebo: 4, and >6: Clonidine: 5 and Placebo: 6; Intensity of headache: Mild: Clonidine: 2 and Placebo: 0; Moderate: Clonidine: 6 and Placebo: 8 and Severe: Clonidine: 20 and Placebo: 19; Duration of headache: < hours: Clonidine: 6 and Placebo: 6, 4-6 hours: Clonidine: 9 and Placebo: 11 and >6 hours: Clonidine: 13 and Placebo: 11	Not reported	Not reported	Not reported	Not reported
Battistella, 1990[3] Design RCT Sample 37 Number analyzed Not reported 51.35% female	Eligible age 7 to 18 years Mean 12.2 years	Criteria of Ad Hoc Committee of the International Headache Society	9 patients had migraine with aura and 28 had migraine without aura	Frequency of attacks/month: Placebo: 3.0+-0.9 and in Nimodipine: 3.3 +-0.9; duration (number of hours/attack):Placebo: 6.9+-2.0 and in Nimodipine: 7.5+-2.0	Not reported	Not reported	Prophylactic treatment was stopped for three months prior to the trial	Not reported

Appendix Table D6. Randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine (continued)

Reference Design Sample Number analyzed % females	Age	Definition of migraine	Presence of aura	Baseline status	Overuse of drugs for acute migraine	Duration of migraine	Prior treatment	Subject compliance and suitability
Battistella, 1993[4] Design RCT Sample 40 Number analyzed Not reported 45% female	Eligible age 7 to 18 years Mean 12.6 years	International Headache Society criteria for migraine	All patients had migraine without aura (inclusion criterion)	History of symptoms(yrs),mean(SD): 4.5(1.3); mean frequency of attacks/month: Trazodone: 4.0+-0.2 and Placebo: 3.5+-0.1; Mean duration of attacks in hours: Trazodone: 20.2+-1.3 and Placebo: 18.2+-1.1	Not reported	4.5 years	Not reported	Not reported
Apostol, 2008[5] Design RCT Sample 305 Number analyzed 299 55% female	Eligible age 12 to 17 years Mean 14.2 years	IHS criteria	Not reported	Migraine headaches within 3 months prior to screening: Mean (SD):Placebo: 16.7 (7.62),250 mg DVPX ER: 16.6 (7.02),500 mg DVPX ER: 18.0 (7.02),1000 mg DVPX ER:17.3 (6.84)	Not reported	Not reported	Not reported	To document compliance with study medication, subjects were instructed to return all medication bottles and pill counts were performed. Site personnel were to counsel any subject with compliance <70%.
Sheridan, 2008[6] Design RCT Sample 305 Number analyzed 299 % females Not reported	Eligible age 12 to 17 years Mean age Not reported	International Headache Society criteria for migraine	Not reported	Mean (SD): Migraine headache rate: Divalproex sodium 250mg: 4.0(1.27); Divalproex sodium 500mg: 3.9(1.28), Divalproex sodium 1000mg: 3.6(1.08), Placebo: 4.0(1.31)	Not reported	Not reported	Not reported	Not reported
Lewis, 2009[7] Design RCT Sample 106 Number analyzed 103 61% female	Eligible age Between 12 and 17 years Mean 14.2 years	International Headache Society guidelines for pediatric migraine	Not reported	Mean migraine attacks, no/month: placebo: 4.1+-1.48; 50mg topiramate: 4.1+-1.74 and 100mg topiramate: 4.3+-1.59 Mean migraine time:d/month: placebo: 6.1+-3.02 ; 50mg	Not reported	Not reported	Not reported	Subjects maintained medication records the accuracy of which was checked by their parents.

Appendix Table D6. Randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine (continued)

Reference Design Sample Number analyzed % females	Age	Definition of migraine	Presence of aura	Baseline status	Overuse of drugs for acute migraine	Duration of migraine	Prior treatment	Subject compliance and suitability
				topiramate: 6.4+-2.86; and 100mg topiramate: 6.9+-3.02				
Winner, 2005[8] Design RCT Sample 162 Number analyzed 157 48.4% female	Eligible age 6 to 15 years Mean 11.1 years	According to International Headache Society classification of pediatric migraine with or without aura	Not reported	Mean (SD) monthly migraine days: topiramate: 5.4(1.7) and placebo: 5.5(2.0)	Not reported	Not reported	Not reported	Not reported
Olness, 1987[9] Design RCT Sample 33 Number analyzed 28 39.3% female	Eligible age 6 to 12 years Mean 9.2 years	Classic migraine, defined as paroxysmal headache associated with all of the following: 1) unilateral head pain, 2) nausea/ vomiting, 3) visual aura (scotomas, visual field defects) or other transitory neurologic disturbance (sensory or motor), and 4) a history of migraine on one of the parents or a sibling.	All children had classic migraine. Therefore, all had migraine with aura.	Not reported	Not reported	Not reported	Not reported	Compliance was monitored by pill counts and maintenance of diaries

Appendix Table D7. Ethical approval, funding, and conflict of interest in randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine

Reference Ethical approval Consent of participants	How project was funded Disclosure of conflict of interest Disclosed relationships
Ludvigsson, 1974[1] Ethical approval: Not reported Consent: Yes	Funding: Not reported Conflict of interest: Not reported
Sillanpää, 1977[2] Ethical approval Not reported Consent: Not reported	Funding: Not reported Conflict of interest: Not reported
Sorge, 1985[10] Ethical approval Not reported Consent: Not reported	Funding: Not reported Conflict of interest: Not reported
Battistella, 1990[3, 11] Ethical approval: Not reported Consent: Not reported	Funding: Not reported Conflict of interest: Not reported
Reference 8436497 Ethical approval: Not reported Consent: Not reported	Funding: Not reported Conflict of interest: Not reported
Reference 18705027 Ethical approval: Yes Consent: Yes	Funding: Industry Conflict of interest: Not reported However, G.Apostol, G.A.Laforet, W.Z.Robieson, E.Olson, W.M.Abi-Saab, and M.Saltarelli are employees of Abbott, Abbott Park, IL,USA
Reference NDA 21168: M02-488 Ethical approval: Yes Consent: Not reported	Funding: Not reported Conflict of interest: Yes All disclosed financial interests were felt to not cause bias in the clinical study outcome
Lewis, 2009[7] Ethical approval: Yes Consent: Yes	Funding: Grant Conflict of interest: Yes Dr Lewis received funds from Abbott Laboratories as a scientific advisor for study design and from Pfizer to attend a scientific advisory meeting in 2004 and received research grants from Abbott Laboratories, Astra Zeneca, Ortho-McNeil and Almirall. Dr Winner received funds from Merck, GlaxoSmithKline, Ortho-McNeil, Pfizer, Allergan, and Astra Zeneca for speaking, advisory board participation, and consultation and received research grants from GlaxoSmithKline, Ortho-McNeil, Pfizer, Allergan, Novartis, Wyeth, Merck, Forest Laboratories, Elan, Minster Pharmaceuticals, MAP Pharmaceuticals, Easai, and ReSearch Pharmaceutical Services. Dr Saper received speaking honoraria from GlaxoSmithKline, Merck, Ortho-McNeil, Neuralieve, Allergan, Medtronic, Pfizer, and Advanced Neuromodulation Systems and received research grants from Pfizer, Endo Pharmaceuticals, GlaxoSmithKline, Neuralieve, ProEthic, Ortho-McNeil, Johnson & Johnson, Merck, Alexa, Allergan, Cypress Pharmaceutical, Advanced Neuromodulation Systems, MAP Pharmacueticals, Medtronic, Torrey Pines Institute for Molecular Studies, and Schwarz Pharma. Drs Ness, Polverejan, Wang, Kurland, Nye, Yuen, Eerdekens, and Ford were employees of Johnson & Johnson.
Winner, 2005[8] Ethical approval: Yes Consent: Yes	Funding: Industry Conflict of interest: Not reported However, Ms Jordan, Dr.Fisher, and Dr.Hulihan are employees of Ortho-McNeil Pharmaceuticals, Raritan, NJ
Olness, 1987[9] Ethical approval: Yes Consent: Yes	Funding: Grant Conflict of interest: Not reported

Appendix Table D8. Risk of bias in randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Reporting of baseline data of the subjects	Adequacy of randomization	Selective outcome reporting	Risk of bias
Ludvigsson, 1974[1]	Double-blind	Not reported	Not reported	No	Not reported	Unclear	Low
Sillanpää, 1977[2]	Double-blind	Not reported	Not reported	Yes	Not reported	Unclear	Low
Sorge, 1985[10]	Double-blind	Not reported	Not reported	Yes	Yes	Unclear	Low
Battistella, 1990[3, 11]	Double-blind	Not reported	Not reported	Yes	Yes	Unclear	Low
Battistella, 1993[4]	Double-blind	Not reported	Not reported	Yes	Not reported	Unclear	Low
Apostol, 2008[5]	Double-blind	Yes	Unclear	Yes	Yes	Unclear	Low
The FDA review[12]	Double-blind	Yes	Not reported	No	Not reported	Though the study mentions about the significance of the results, there are no results displayed	Low
Lewis, 2009[7]	Double-blind	Yes	Clearly adequate	Yes	Adequate	Unclear	Low
Winner, 2005[8]	Double-blind	Yes	Unclear	Yes	Not adequate. In the placebo group the % of white children was 87.8 and black children was 10.2, whereas in the topiramate group the % of white children was 72.2 and black children was 25.9	Unclear	Moderate
Olness, 1987[9]	Not reported	Not reported	Not reported	Yes	Yes	Unclear	Unclear

Appendix Table D9. Strength of evidence of migraine prevention with antiepileptic topiramate in children (results from randomized controlled clinical trials)

Outcome	Dose	Rate Drug [placebo]	RCTs	Children	Directness	Risk of bias	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Reduction of baseline headache frequency by >50%	200mg/day	61.2 [45.8]	2	230	Yes	Moderate	Yes	Yes	Not applicable	Moderate	Topiramate , 200mg/day, did not increase rate of reduction in migraine by 50%
	100mg/day	45.7 [45.5]	1	68	Yes	Low	NA	Yes	Not applicable	Low	Topiramate , 100mg/day, did not increase rate of reduction in migraine by 50%
	100-200mg/day	58.2 [45.7]	2	298	Yes	Moderate	Yes	Yes	No	Moderate	Topiramate , 100-200mg/day, did not increase rate of reduction in migraine by 50%

Appendix Table D10. Reduction in frequency of migraine attack by at least 50% from baseline with topiramate versus placebo in children (pooled with random effects results from randomized controlled clinical trials)

Reference Dose of drug	Events/ randomized active	Events/ randomized control	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight	Risk of bias
200mg/day							
Winner, 2005[8] 50 mg/day at week 3, titrated to a max dose of 200 mg/day (2-3kg mg/kg/day)	61/112	23/50	1.18 (0.84; 1.67)	39.71	0.09 (-.08; .25)	37.29	Moderate
Lewis, 2009[7] 25mg/day initially and then gradually increased to 100mg/day, dosed twice daily at the investigator's discretion	29/35	15/33	1.82 (1.22; 2.73)	34.41	0.37 (.16; .59)	32.65	Low
Pooled			1.45 (0.95; 2.21)	74.12	0.22 (-.06; .51)	69.94	
100 mg/day							
Lewis, 2009[7] 25mg/day initially and then gradually increased to 50mg/day, dosed twice daily at the investigator's discretion	16/35	15/33	1.01 (0.60; 1.69)	25.88	0.00 (-.23; .24)	30.06	Low
Pooled			1.32 (0.94; 1.84)	100	0.15 (-.06; .37)	100	

Appendix Table D11. Efficacy of topiramate on migraine prevention, individual RCTs

Drug Dose	Definition of the outcome	Reference Risk of bias	Events/randomized with drug	Events/randomized with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Topiramate 50 mg/day at week 3, titrated to a max dose of 200 mg/day (2-3kg mg/kg/day)	≥75% reduction in monthly migraine days	Winner, 2005[8] Moderate	36/112	7/50	**2.3 (1.1; 4.8)**	**0.18 (0.05: 0.31)**
	≥75% reduction in monthly migraine days during the last 28 days of treatment	Winner, 2005[8] Moderate	57/112	15/50	**1.7 (1.1; 2.7)**	**0.21 (0.05: 0.37)**

Bold - significant difference at 95% confidence level

Appendix Table D12. Reduction in migraine days with topiramate versus placebo in children (pooled with random effects results from randomized controlled clinical trials)

Reference Dose of topiramate	Outcome with drug [Standard deviation]	Outcome with placebo [Standard deviation]	Standardized mean difference (95% CI)	Weight	Mean ratio (95%CI)	Weight	Risk of bias
Winner, 2005[8] 50 mg/day at week 3, titrated to a max dose of 200 mg/day (2-3kg mg/kg/day)	-2.6 [2.6]	-2.0 [3.1]	-0.22 (-.55; 0.12)	58.4	1.30 (0.81; 2.08)	35.41	Moderate
Lewis, 2009[7] 25mg/day initially and then gradually increased to 100mg/day, dosed twice daily at the investigator's discretion	-75.9 [32.42]	-49.7 [46.06]	-0.66 (-1.15; -0.17)	41.6	**1.53 (1.08; 2.16)**	64.59	Low
Pooled			-0.40 (-0.83; 0.03)	100	**1.44 (1.09; 1.91)**	100	
Lewis, 2009[7] 25mg/day initially and then gradually increased to 50mg/day, dosed twice daily at the investigator's discretion	-52.5 [48.55]	-49.7 [46.06]	-0.06 (-0.54; 0.42)	100	1.06 (0.68; 1.64)	100	Low
Pooled			-0.30 (-0.61; 0.02)		**1.32 (1.04; 1.67)**		Moderate

Bold - significant difference at 95% confidence level

Appendix Table D13. Strength of evidence of migraine prevention with antiepileptic divalproex sodium in children (results from randomized controlled clinical trials)

Drug	Outcome	Dose	Rate	RCTs	Children	Direct	Risk of bias	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Divalproex sodium	Reduction of baseline headache frequency by >50%	250-1000 mg/day	40-50 [45]	1	305	Yes	Low Double blind	Yes	Yes	No	Low	Divalproex sodium, 250-100mg/day did not increase rate of reduction in migraine by 50%

Appendix Table D14. Reduction in frequency of migraine attack by at least 50% from baseline with divalproex sodium versus placebo in children (results from randomized controlled clinical trials)

Drug Dose	Definition of the outcome	Reference Risk of bias	Events/randomized with drug	Events/randomized with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Divalproex sodium 250mg once daily	≥50% reduction in 4 week migraine rate	Apostol, 2008[5] Low	33/83	33/73	0.9 (0.6; 1.3)	-0.05 (-0.21: 0.10)
Divalproex sodium 500mg once daily. For the first 2 weeks dose was 250mg/day	≥50% reduction in 4 week migraine headache rate	Apostol, 2008[5] Low	27/74	33/73	0.8 (0.5; 1.2)	-0.09 (-0.25: 0.07)
Divalproex sodium 1000 mg once daily. For the first 2 weeks dose was 500 mg/day	≥50% reduction in 4 week migraine headache rate	Apostol, 2008[5] Low	37/75	33/73	1.1 (0.8; 1.5)	0.04 (-0.12: 0.20)

Appendix Table D15. Reduction in migraine days with divalproex sodium versus placebo in children (pooled with random effects results from randomized controlled clinical trials)

Reference Dose of divalproex sodium	Outcome with drug [Standard deviation]	Outcome with placebo [Standard deviation]	Standardized mean difference (95% CI)	Weight	Mean ratio (95% CI)	Weight	Risk of bias
Apostol, 2008[5] 250mg once daily	-2.8 [2.91]	-2.8 [3.02]	0.00 (-0.31; 0.31)	49.12	1.00 (0.72; 1.40)	49.12	Low
Sheridana, 2008[6] 250mg/day	1.6 [1.7]	1.7 [1.74]	-0.06 (-0.37; 0.26)	50.88	0.94 (0.68; 1.31)	50.88	Low
Pooled			-0.03 (-0.25; 0.19)	100	0.97 (0.77; 1.23)	100	Low
500mg/day							
Apostol, 2008[5] 500mg once daily. For the first 2 weeks dose was 250mg/day	-2.2 [3.18]	-2.8 [3.02]	0.19 (-0.13; 0.52)	39.45	0.79 (0.52; 1.19)	39.45	
Sheridan, 2008[6] 500mg/day	1.5 [1.55]	1.7 [1.74]	-0.12 (-0.45; 0.20)	60.55	0.88 (0.63; 1.23)	60.55	Low
Pooled			0.04 (-0.27; 0.34)	100	0.84 (0.65; 1.09)	100	Low
1000 mg/day							
Apostol, 2008[5] 1000 mg once daily. For the first 2 weeks dose was 500 mg/day	-3.1 [3.61]	-2.8 [3.02]	-0.09 (-0.41; 0.23)	46.3	1.11 (0.77; 1.59)	46.3	
Sheridan, 2008[6] 1000mg/day	1. 5 [1.59]	1.7 [1.74]	-0.12 (-0.44; 0.20)	53.7	0.88 (0.63; 1.23)	53.7	Low
Pooled			-0.11 (-0.33; 0.12)	100	0.98 (0.77; 1.25)	100	Low
Pooled			-0.03 (-0.16; 0.10)		0.93 (0.81; 1.08)		Low

Appendix Table D16. Percentage of migraine headaches treated with symptomatic medications with divalproex sodium versus placebo in children, individual low risk of bias randomized controlled clinical trial[5]

Dose	Mean [Standard deviation) with drug, %	Mean [Standard deviation) with placebo, %	Mean difference, % (95% CI)	Cohen standardized mean difference (95% CI)	Means ratio (95% CI)
250mg once daily	-7.1 [34.0]	-9.7 [22.5]	2.6 (-6.3; 11.5)	0.09 (-0.23;0.40)	0.7 [0.6]
500mg once daily. For the first 2 weeks dose was 250mg/day	-8.0 [29.6]	-9.7 [22.5]	1.7 (-6.8; 10.2)	0.06 (-0.26;0.39)	0.8 [0.5]
1000 mg once daily. For the first 2 weeks dose was 500 mg/day	-8.5 [35.9]	-9.7 [22.5]	1.2 (-8.4; 10.8)	0.04 (-0.28;0.36)	0.9 [0.6]

Appendix Table D17. Reduction in migraine days and duration with antidepressant trazodone vs. placebo (results from low risk of bias randomized controlled clinical trial)[4]

Definition of the outcome	Dose	Mean [STD) with drug	Mean [STD) with placebo	Mean difference, (95% CI)	Cohen standardized mean difference (95% CI)	Mean ratio (95% CI)
Frequency of headache attacks/month	1mg/kg/day divided into 3 doses	2.8 [0.2]	1.2 [0.2]	**1.6 (1.5 to 1.7)**	**8.00 (6.10 to 9.90)**	2.3 [0.04]
Duration: number of hours/attack	1mg/kg/day divided into 3 doses	13.1 [1.3]	4.9 [0.7]	**8.2 (7.6 to 8.8)**	**7.85 (5.98 to 9.73)**	2.7 [0.04]

Bold - significant differences at 95% confidence level

Appendix Table D18. Strength of evidence of migraine prevention with propranolol in children (results from randomized controlled clinical trials)

Outcome	Dose	Rate Drug [placebo]	RCTs	Children	Directness	Risk of bias Masking of treatment	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Complete cessation of headache attacks	60mg-120mg/day	85 [14]	1	32	Yes	Low Double blind	Not applicable	Yes	Not applicable Large effect	Low	Propranolol Increased rates of complete cessation of headache attacks
Mean number of headaches	3mg/kg/d	Not applicable	1	33	Yes	Unclear Not reported	Not applicable	Yes	Not applicable	Insufficient	Propranolol did not decrease number of migraine days

Appendix Table D19. Reduction in frequency of migraine attack with propranolol versus placebo in children, individual low risk of bias randomized controlled clinical trial[1]

Dose	Definition of the outcome	Events/ randomized [rate] Propranolol	Events/ randomized [rate] Placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Propranolol 60mg/day in three divided doses for children weighing less than 35 kg and 120mg/day in three divided doses for children weighing 35kg or more	Excellent degree of improvement before cross-over at 13 weeks (Excellent: No headache or only negligible symptoms remain)	9/13 [0.69]	1/15 [0.067]	**10.4 (1.5 to 71.4)**	**0.63 (0.34 to 0.91)**
	Excellent degree of improvement after cross-over at 26 weeks (Excellent: No headache or only negligible symptoms remain)	11/13 [0.85]	2/15 [0.14]	**6.3 (1.7 to 23.5)**	**0.71 (0.45 to 0.97)**
	Good degree of improvement before cross-over at 13 weeks (Good = Frequency of attacks reduced to <1/3 before cross-over at 13 weeks)	2/13 [0.154]	1/15 [0.07]	2.3(0.2 to 22.6)	0.09 (-0.15 to 0.32)
	Good degree of improvement after cross-over at 26 weeks (Good = Frequency of attacks reduced to <1/3)	1/13	0/15	3.4(0.2 to 77.6)	0.08 (-0.11 to 0.26)

Bold- significant improvement at 95% confidence level

Appendix Table D20. Mean number of headaches per 3 month study period with propranolol versus placebo in children, individual unclear risk of bias randomized controlled clinical trial[9]

Dose	Mean [STD] with propranolol	Mean [STD] with placebo	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)	Means ratio (95% CI)
3mg/kg/d in three divided doses	14.9 [12.9]	13.3 [9.5]	1.6 (-4.3 to 7.5)	0.14 (-0.38 to 0.67)	1.1 [0.2]

Appendix Table D21. Reduction in migraine days and duration with selective calcium channel blocker nimodipine vs. placebo (results from low risk of bias randomized controlled clinical trial)[3]

Dose	Definition of outcome	Mean [STD) with drug	Mean [STD) with placebo	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)	Means ratio (95% CI)
10 to 20mg three times daily (<40kg to 10mg=5 drops TIS to 40-50 kg to 16mg=8 drops TID to >50kg to 20mg=10 drops TID)	Frequency of headache attacks/month	2.8 [0.6]	1.9 [0.7]	**0.9 (0.5 to 1.3)**	1.38 (0.66 to 2.10)	1.5 [0.1]
	Duration to number of hours/attacks	5.0 [1.2]	4.4 [1.1]	0.6 (-0.1 to 1.3)	0.52 (-0.13 to1.18)	1.1 [0.1]

Bold - significant differences at 95% confidence level

Appendix Table D22. Strength of evidence of migraine prevention with clonidine, 25-50µg/day in children

Outcome	Rate Drug [Placebo]	RCTs, Reference	Children	Directness	Risk of bias	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Reduction of baseline headache frequency	11 [24]	1 Sillanpää, 1977[2]	57	Yes	Low	NA	Yes	NA	Low	Clonidine did not increase rates of complete cessation or clinically important reduction of headache attacks
Reduction in acute drug utilization	50 [35]	1 Sillanpää, 1977[2]	57	Yes	Low	NA	Yes	NA	Low	Clonidine did not decrease acute drug utilization
Reduction in migraine severity	25 [14]	1 Sillanpää, 1977[2]	57	Yes	Low	NA	Yes	NA	Low	Clonidine did not decrease rate of mild migraine

Appendix Table D23. Reduction in frequency of migraine and severity with clonidine versus placebo in children (results from individual double blind low risk of bias randomized controlled clinical trial)[2]

Dose	Definition of the outcome	Events/ Randomized [Rate] Propranolol,%	Events/ Randomized [Rate] Placebo,%	Relative risk (95% CI)	Absolute risk difference (95% CI)
Clonidine 25µg once daily to children weighing 40kg or less and 25µg twice daily to those weighing more than 40kg	5-6: Headache frequency/month after treatment	2/28	0/29	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
	Zero: Headache frequency/month after treatment	3/28	7/29	0.4 (0.1 to 1.5)	-0.13 (-0.33 to 0.06)
	1-2: Headache frequency/month after treatment	9/28	8/29	1.2 (0.5 to 2.6)	0.05 (-0.19 to 0.28)
	3-4: Headache frequency/month after treatment	6/28	4/29	1.6 (0.5 to 4.9)	0.08 (-0.12 to 0.27)
	Duration of headaches: >6 hours	6/28	5/29	1.2 (0.4 to 3.6)	0.04 (-0.16 to 0.25)
	Duration of headaches: 4-6 hours	5/28	2/29	2.6 (0.5 to 12.3)	0.11 (-0.06 to 0.28)
	Intensity of headache: moderate	7/28	5/29	1.5 (0.5 to 4.0)	0.08 (-0.13 to 0.29)
	Intensity of headache: severe	5/28	4/29	1.3 (0.4 to 4.3)	0.04 (-0.15 to 0.23)
	Intensity of headache: mild	7/28	4/29	1.8 (0.6 to 5.5)	0.11 (-0.09 to 0.32)
	Duration of headaches: <4 hours	6/28	6/29	1.0 (0.4 to 2.8)	0.01 (-0.20 to 0.22)
	Reduction for need for temporary drug therapy for single attacks	14/28	10/29	1.5 (0.8 to 2.7)	0.16 (-0.10 to 0.41)

Appendix Table D24. Randomized controlled clinical trials that examined comparative effectiveness drugs for migraine prevention in children

Reference Total sample assigned to treatment Number analyzed % females	Question the study expects to answer	Age Definition of migraine Presence of aura	Baseline migraine status: Comorbidity Concurrent medication Overuse of drugs for acute migraine	Duration of migraine Prior treatment Subject compliance and suitability
Ashrafi, 2005[13] Design RCT Sample 120 Number analyzed Not reported 33.9% females	To compare the effect of sodium valproate with that of propranolol in pediatric migraine prophylaxis	3 to 15 years 1988 International Headache Society criteria for pediatric common migraine All patients had migraine without aura	Mean headache frequency/month: sodium valproate: 7.8 and propranolol: 7.9 Not reported Not reported Not reported	Not reported Not reported Not reported
Bidabadi, 2010[14] Design RCT Sample 63 Number analyzed 60 33% females	To compare the efficacy and tolerability of propranolol and sodium valproate in the prevention of migraine in the pediatric population	5-15 years The diagnostic criteria for pediatric migraine without aura as defined by the International Headache Society (IHS). Not reported	Mean headache frequency per month: propranolol: 13.86 and sodium valproate: 13.23 Not reported Not reported Not reported	Not reported Not reported Monthly follow-up
Unalp, 2008[15] Design RCT Sample 48 Number analyzed 48 54.17% females	To compare the efficacy of topiramate and sodium valproate for the prevention of pediatric migraine, retrospectively	Not reported International Headache Society 2004 criteria for migraine headache Not reported	Duration of migraine episode, h: Sodium valproate: 10.2 (9.4), Topiramate: 7 (12); Headache frequency/month: Sodium valproate: 15.3 (10.1), Topiramate: 20.1 (10.2); Headache intensity, VAS: Sodium valproate: 6.8 (1) and Topiramate: 71 (1) Not reported Not reported Not reported	Not reported Not reported Not reported

Appendix Table D25. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness drugs for migraine prevention in children

Reference	Funding	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests—relationship
Ashrafi, 2005[13]	Not reported	Not reported	Not reported	Not reported	
Bidabadi, 2010[14]	None	Yes	Yes	None	Not applicable
Unalp, 2008[15]	No support	Yes	Not reported	None	

Appendix Table D26. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness drugs for migraine prevention in children

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Ashrafi, 2005[13]	Not reported	Not reported	Not reported	Yes	Unclear	Unclear
Bidabadi, 2010[14]	Double-blind	No	Unclear	Yes	Unclear	Moderate
Unalp, 2008[15]	Not reported	Not reported	Not reported	Yes	Unclear	Unclear

Appendix Table D27. Comparative effectiveness of sodium valproate versus propranolol in preventing migraine in children (pooled with random effects models results from randomized controlled clinical trials)

Outcome	Reference Risk of bias	Active drug Dose vs. control drug, Dose	Events/randomized [rate of outcome in active group], %	Events/randomized [rate of outcome in control group], %	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Reduction in frequency of migraine attack by at least 50% from baseline	Ashrafi, 2005[13] Risk of bias Unclear	Sodium valproate,10-40mg/kg/day vs. Propranolol,1-3 mg/kg/day in two divided doses	43/60 [72]	41/60 [69]	1.0 (0.8; 1.3)	54.62	0.03 (-0.13; 0.20)	54.2
	Bidabadi, 2010[14] Risk of bias Moderate	Sodium valproate,15 - 30mg/kg/day vs. Propranolol,2-3mg/kg/day	20/31 [64.5]	27/32 [84.4]	0.8 (0.6; 1.0)	45.38	-0.20 (-0.41; 0.01)	45.8
		Pooled	63/91 [69.5]	68/92 [74.4]	0.9 (0.7; 1.2)	100	-0.07 (-0.30; 0.15)	100
	Ashrafi, 2005[13] Risk of bias Unclear	Sodium valproate,10-40mg/kg/day vs. Propranolol,1-3 mg/kg/day in two divided doses	13/60 [21]	10/60 [17]	1.3 (0.6; 2.7)	78.36	0.05 (-0.09; 0.19)	54.81
	Bidabadi, 2010[14] Risk of bias Moderate	Sodium valproate,15 - 30mg/kg/day vs. Propranolol,2-3mg/kg/day	3/31 [9.68]	4/32 [12.5]	0.8 (0.2; 3.2)	21.64	-0.03 (-0.18; 0.13)	45.19
		Pooled	16/91 [17.1]	14/92 [15.4]	1.2 (0.6; 2.2)	100	0.02 (-0.09; 0.12)	100

Appendix Table D28. Comparative effectiveness of sodium valproate versus propranolol in preventing migraine in children (results from individual randomized controlled clinical trials)

Definition of the outcome	Active versus control drug	Reference Risk of bias	Events/randomized in active Control group Rate in active [control] group, %	Relative risk (95% CI)	Absolute risk difference (95% CI)
Reduction of headache severity by at least one grade	Sodium valproate, 15-30mg/kg/day vs. Propranolol, 2-3mg/kg/day	Bidabadi, 2010[14] Risk of bias: Moderate	17/31 20/32 54.8 [62.5]	0.9 (0.6; 1.3)	-0.08 (-0.32; 0.17)
Reduction of headache duration	Sodium valproate, 10-40mg/kg/day vs. Propranolol, 1-3 mg/kg/day in two divided doses	Ashrafi, 2005[13] Risk of bias: Unclear	31/60 32/60 52.0 [53.0]	1.0 (0.7; 1.4)	-0.02 (-0.20; 0.16)
Reduction of baseline headache frequency by >70%	Sodium valproate,15-30mg/kg/day vs. Propranolol, 2-3mg/kg/day	Bidabadi, 2010[14] Risk of bias: Moderate	10/31 21/32 32.3 [65.6]	**0.5 (0.3; 0.9)**	**-0.33 (-0.57; -0.10)**
Reduction of baseline headache frequency by 50-70%	Sodium valproate,15-30mg/kg/day vs. Propranolol, 2-3mg/kg/day	Bidabadi, 2010[14] Risk of bias: Moderate	9/31 4/32 29.0 [12.5]	2.3 (0.8; 6.8)	0.17 (-0.03; 0.36)
Better response to rescue medications	Sodium valproate, 10-40mg/kg/day vs. Propranolol, 1-3 mg/kg/day in two divided doses	Ashrafi, 2005[13] Risk of bias: Unclear	37/60 40/60 61.0 [67.0]	0.9 (0.7; 1.2)	-0.05 (-0.22; 0.12)
Reduction of baseline headache frequency by 20-50%	Sodium valproate,15-30mg/kg/day vs. Propranolol, 2-3mg/kg/day	Bidabadi, 2010[14] Risk of bias: Moderate	7/31 3/32 22.6 [9.4]	2.4 (0.7; 8.5)	0.13 (-0.05; 0.31)
Reduction of baseline headache frequency by <20%	Sodium valproate,15-30mg/kg/day vs. Propranolol, 2-3mg/kg/day	Bidabadi, 2010[14] Risk of bias: Moderate	4/31 2/32 12.9 [6.3]	2.1 (0.4; 10.5)	0.07 (-0.08; 0.21)
Reduction of headache severity at least for one grade	Sodium valproate, 10-40mg/kg/day vs. Propranolol, 1-3 mg/kg/day in two divided doses	Ashrafi, 2005[13] Risk of bias: Unclear	34/60 38/60 56.0 [64.0]	0.9 (0.7; 1.2)	-0.07 (-0.24; 0.11)

Bold - significant differences at 95% confidence level

Appendix Table D29. Comparative effectiveness of topiramate versus sodium valproate in preventing migraine in children (results from a randomized controlled clinical trial)[15]

Definition of the outcome	Active vs. control drug	Level of outcome [STD] /number of subjects in active group and control group	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Headache frequency/month: After therapy	Topiramate, 1-3mg/kg vs. sodium valproate, 10-15mg/kg	4.4 [5.5]/28 5.5 [6.6]/20	-2.20 (-6.48; 2.08)	-0.32 (-0.89; 0.26)
Headache intensity (VAS): After therapy	Topiramate, 1-3mg/kg vs. sodium valproate, 10-15mg/kg	3.2 [1.8]/28 1.8 [3.4]/20	-0.20 (-1.34; 0.94)	-0.10 (-0.68; 0.47)
Duration of migraine episode (h)	Topiramate, 1-3mg/kg vs. sodium valproate, 10-15mg/kg	2.4 [3.1]/28 3.1 [1.4]/20	1.00 (-0.59; 2.59)	0.35 (-0.23; 0.93)
PedMIDAS (Pediatric Migraine Disability Assessment Score)	Topiramate, 1-3mg/kg vs. sodium valproate, 10-15mg/kg	4.6 [6.5]/28 6.5 [5.5]/20	-0.90 (-5.60; 3.80)	-0.12 (-0.69; 0.46)

Appendix Table D30. Randomized controlled clinical trials that examined comparative effectiveness of drugs versus active nonpharmacological treatments for migraine prevention in children

Reference Design Sample Analyzed % female	Aim	Age	Definition of migraine	Presence of aura	Baseline status of subjects: disease	Duration of migraine	Subject compliance and suitability
Olness, 1987[9] Design RCT Sample 33 Number of analyzed 28 39.3% female	Propranolol, vs. self-hypnosis	6-12 years Mean 9.2 years	Classic migraine.	All children had classic migraine. Therefore, all had migraine with aura.	Not reported	Not reported	Compliance was monitored by pill counts and maintenance of dairies
Sartory, 1998 Design RCT Sample 43 Number of analyzed 43 39.5% female	Metaprololvs. progressive relaxation training and vasomotor feedback	8-16 years Mean 11.3 years	IHS criteria	16 37.2% children had migraine with aura	Headache frequency/ week: relaxation group: 2.24 (1.89), vasomotor feedback group: 1.77 (1.17), and metoprolol group: 1.33 (0.62)	4.7 years	Not reported

Appendix Table D31. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of drugs versus active nonpharmacological treatments for migraine prevention in children

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interests-relationship
Olness, 1987[9]	Grant	Yes	Yes	Not reported	
Sartory, 1998[16]	Other	Not reported	Yes	Not reported	Not applicable

Appendix Table D32. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of drugs versus active nonpharmacological treatments for migraine prevention in children

Reference	Masking of the treatment status	Intention to treat analysis preplanned	Allocation concealment	Reporting of baseline data of subjects	Adequacy of randomization	Selective outcome reporting	Risk of bias
Olness, 1987[9]	Not reported	Not reported	Not reported	Yes	Yes	Unclear	Unclear
Sartory, 1998[16]	Not reported	Not reported	Unclear	Yes	Not adequate	Unclear	Unclear

Appendix Table D33. Comparative effectiveness of metoprolol and nonpharmacological treatments in unclear risk of bias randomized controlled clinical trial relative to absolute risks[16]

Active drug and dose	Nonpharmacological treatment	Definition of the outcome	Events/randomized in active and control Rate of outcome in active [control]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half of this dose was given.	Progressive relaxation training + stress management	Percentage of patients who improved by more than 50% in the headache index (percent change from baseline to post-treatment of frequency *intensity of headache episodes)	5/13 12/15 38.5 [80.0]	0.5 (0.2 to 1.0)	-0.42 (-0.75 to -0.08)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half of this dose was given.	Cephalic vasomotor feedback + stress management	Percentage of patients who improved by more than 50% in the headache index (percent change from baseline to post-treatment of frequency *intensity of headache episodes)	5/13 8/15 38.5 [53.3]	0.7 (0.3 to 1.7)	-0.15 (-0.51 to 0.22)

Appendix Table D34. Comparative effectiveness of metoprolol and nonpharmacological treatments in unclear risk of bias randomized controlled clinical trial, mean differences[16]

Active drug and dose	Nonpharmacological treatment	Definition of the outcome	Mean [standard deviation] with drug	Mean [standard deviation} with nondrug	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half his dose was given.	Progressive relaxation training + stress management	Frequency of headache at 8 month followup	1.25 [0.82]	1.14 [1.19]	0.11 (-0.64 to 0.86)	0.11 (-0.64 to 0.85)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half his dose was given.	Progressive relaxation training + stress management	Frequency of headache at 8 month followup	1.25 [0.82]	1.05 [0.72]	0.20 (-0.38 to 0.78)	0.26 (-0.49 to 1.01)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half his dose was given.	Progressive relaxation training + stress management	Intensity of headache at 8 month followup (intensity was measured on a scale of 1 (light) to 10 (overbearing))	4.19 [2.42]	3.09 [1.67]	1.10 (-0.46 to 2.66)	0.54 (-0.22 to 1.29)
Metoprolol 50mg once daily in children <40kg body weight and 100mg in children >40kg. During first week of treatment half his dose was given.	Progressive relaxation training + stress management	Intensity of headache at 8 month followup (intensity was measured on a scale of 1 (light) to 10 (overbearing))	4.19 [2.42]	2.98 [2.65]	1.21 (-0.67 to 3.09)	0.48 (-0.28 to 1.23)

Appendix Table D35. Comparative effectiveness of propranolol and self-hypnosis in unclear risk of bias randomized controlled clinical trial[9]

Active drug and dose	Non pharmacological treatment	Definition of the outcome	Mean [Standard deviation] with drug	Mean [Standard deviation} with non drug	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Propranolol 3mg/kg/d in three divided doses	Olness, 1987[9] Self-hypnosis	Mean number of headaches per 3 month study period	14.90 [12.9]	5.80 [5.8]	9.10 (3.86 to 14.34)	0.91 (0.36 to 1.46)

Appendix Table D36. Randomized controlled clinical trials that examined dose response effectiveness of drugs for migraine prevention in children

Reference Sample Total number analyzed % females	Eligible age Mean age	Definition of migraine	Presence of aura	Baseline status of subjects: disease	Duration of migraine
Winner, 2006[17] Sample 51 Number analyzed 49 71% females	Eligible age 12-17 years Mean age 14 years	International Headache Society criteria	Not reported	Migraine frequency, Mean (SD): Topiramate 50mg/day: 4.8 (1.9), Topiramate 100mg/day: 6.2 (3.5), Topiramate 200mg/day: 4.9 (2.0);	Not reported
Lewis, 2007[18] Sample 14 Number analyzed 14 71.43% females	Eligible age 6 to 18 years Mean age 13.43 years	According to ICHD-2 criteria for basilar migraine	100% of patients had aura; 8 of 14 patients also had periodic attacks of migraine without aura	Average number of migraines per month, median: 25mg group: 8 and 100mg/d group: 5 ; Average severity of migraine, mean (SD), 0-5 point scale: 25mg group: 3.37 (0.53) and 100mg group: 3.4 (0.67)	4.2 years
Pandina, 2010[19] Sample 103 Number analyzed 103 61% females	Eligible age 12-17 years Mean age 14.2 years	International Headache Society criteria for pediatric migraine	Not reported	Not reported	Not reported
Apostol, 2008[5] Sample 305 Number analyzed 299 55% females	Eligible age 12-17 years Mean age 14.2 years	IHS criteria	Not reported	Migraine headaches within 3 months prior to screening: Mean (SD):Placebo: 16.7 (7.62), 250 mg DVPX ER: 16.6 (7.02), 500 mg DVPX ER: 18.0 (7.02), 1000 mg DVPX ER:17.3 (6.84)	Not reported
Lewis, 2009[7] Sample 106 Number analyzed 103 61% females	Eligible age Between 12 and 17 years Mean age 14.2 years	International Headache Society guidelines for pediatric migraine	Not reported	Mean migraine attacks, no/month: placebo: 4.1±1.48; 50mg topiramate: 4.1±1.74 and 100mg topiramate: 4.3±1.59 Mean migraine time:d/month: placebo: 6.1±3.02; 50mg topiramate: 6.4±2.86; and 100mg topiramate: 6.9±3.02	Not reported
Sheridan, 2008[6] Sample 305 Number analyzed 299 % females Not reported	Eligible age 12-17 years Mean age Not reported	International Headache Society criteria for migraine	Not reported	Mean (SD): Migraine headache rate: Divalproex sodium 250mg: 4.0(1.27); Divalproex sodium 500mg: 3.9 (1.28), Divalproex sodium 1000mg: 3.6 (1.08), Placebo: 4.0(1.31)	Not reported

Appendix Table D37. Funding and conflict of interest in randomized controlled clinical trials that examined dose response effectiveness of drugs for migraine prevention in children

Reference	How project was funded	Ethical approval of study	Consent of participants	Conflict of interest	Conflict of interest—relationship
Winner, 2006[17]	Industry	Yes	Yes	Yes	Drs. Winner and Gendolla have received consulting and speaker fees from Johnson & Johnson. Drs. Stayer, Wang, Yuen, Battisti, and Nye are employees of the company.
Lewis, 2007[18]	Industry	Yes	Yes	Yes	The study was supported by a research grant from Ortho-McNeil Neurologies Inc. as an investigator-initiated project.
Pandina, 2010[19]	Industry	Yes	Yes	Yes	George Rogan MS, of Phase Five Communications, Inc. helped to coordinate, edit, and finalize the manuscript for submission
Apostol, 2008[5]	Industry	Yes	Yes	Not reported	Not reported, however, G. Apostol, G.A. Laforet, W.Z. Robieson, E. Olson, W.M. Abi-Saab, and M. Saltarelli are employees of Abbott, Abbott Park, IL, USA
Lewis, 2009[7]	Grant	Yes	Yes	Yes	Dr. Lewis received funds from Abbott Laboratories as a scientific advisor for study design and from Pfizer to attend a scientific advisory meeting in 2004 and received research grants from Abbott Laboratories, Astra Zeneca, Ortho-McNeil and Almirall. Dr Winner received funds from Merck, GlaxoSmithKline, Ortho-McNeil, Pfizer, Allergan, and Astra Zeneca for speaking, advisory board participation, and consultation and received research grants from GlaxoSmithKline, Ortho-McNeil, Pfizer, Allergan, Novartis, Wyeth, Merck, Forest Laboratories, Elan, Minster Pharmaceuticals, MAP Pharmaceuticals, Easai, and ReSearch Pharmaceutical Services. Dr. Saper received speaking honoraria from GlaxoSmithKline, Merck, Ortho-McNeil, Neuralieve, Allergan, Medtronic, Pfizer, and Advanced Neuromodulation Systems and received research grants from Pfizer, Endo Pharmaceuticals, GlaxoSmithKline, Neuralieve, ProEthic, Ortho-McNeil, Johnson & Johnson, Merck, Alexa, Allergan, Cypress Pharmaceutical, Advanced Neuromodulation Systems, MAP Pharmacueticals, Medtronic, Torrey Pines Institute for Molecular Studies, and Schwarz Pharma. Drs Ness, Polverejan, Wang, Kurland, Nye, Yuen, Eerdekens, and Ford were employees of Johnson & Johnson.
Sheridan, 2008[6]	Not reported	Yes	Not reported	Yes	All disclosed financial interests were felt to not cause bias in the clinical study outcome

Appendix Table D38. Risk of bias in randomized controlled clinical trials that examined dose response effectiveness of drugs for migraine prevention in children

Reference	Masking of treatment status	Intention to treat analysis preplanned	Allocation concealment	Adequacy of randomization	Selective outcome reporting	Risk of bias
Winner, 2006[17]	Double-blind	Yes	Clearly adequate (computer-generated randomization schedule)	Not adequate (Topiramate 100mg had higher mean frequency and days of migraine compared to other groups and topiramate 200mg had higher percentage of men and women compared to other groups)	Unclear	Low
Lewis, 2007[18]	Double-blind	Yes	Unclear	Adequate	Unclear	Low
Pandina, 2010[19]	Double-blind	Yes	Not reported	Yes	Unclear	Low
Apostol, 2008[5]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Lewis, 2009[7]	Double-blind	Yes	Clearly adequate	Adequate	Unclear	Low
Sheridan, 2008[6]	Double-blind	Yes	Not reported	Not reported	Though the study mentions the significance of the results, there are no results displayed	Low

Appendix Table D39. Dose response effects with topiramate in preventing migraine in children (results from randomized controlled clinical trials)

Compared daily doses	Outcomes	Reference	Events/ randomized with higher dose	Events/ randomized with lower dose	Relative risk (95% CI)	Absolute risk difference 995% CI)
Topiramate 25mg vs. 100mg	Overall Parent Global Assessment: Much improved	Lewis, 2007[18]	2/7	0/7	5.0 (0.3to 88.5)	0.29(-0.08 to 0.65)
	Overall Parent Global Assessment: Very much improved	Lewis, 2007[18]	4/7	3/7	1.3 (0.5to 3.9)	0.14(-0.38 to 0.66)
	Overall Parent Global Assessment: Minimally improved	Lewis, 2007[18]	0/7	1/7	0.3 (0.0 to 7.0)	-0.14(-0.46 to 0.18)
	Overall Parent Global Assessment: No change	Lewis, 2007[18]	1/7	2/7	0.5 (0.1 to 4.3)	-0.14(-0.57 to 0.28)
	Greater than 50% reduction in migraine frequency	Lewis, 2007[18]	7/7	5/7	1.4 (0.8 to 2.2)	0.29(-0.08 to 0.65)
	Responder, that is, ≥50% reduction in the monthly migraine attack rate	Lewis, 2009[7]	16/35	29/35	**0.6 (0.4 to 0.8)**	**-0.37(-0.58 to -0.16)**

Bold - significant difference at 95% confidence level

Appendix Table D40. Dose response reduction in migraine intermediate outcomes with topiramate in children, the results from randomized controlled clinical trials

Compared doses	Outcome	Reference	Mean [Standard deviation] with higher dose	Mean [Standard deviation] with lower dose	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Topiramate 25mg vs. 100mg	Difference in PedMIDAS score of headache disability: grade I is 0-10 (none to mild) to grade IV is >50 (severe).	Lewis, 2007[18]	-35.1 [22.4]	-23.3 [28.3]	-11.85 (-38.59 to 14.89)	-0.46 (-1.53 to 0.60)
	Difference in average monthly basilar migraine days from baseline	Lewis, 2007[18]	-3.0 [2.5]	-1.9 [2.8]	-1.03 (-3.76 to 1.70)	-0.39 (-1.45 to 0.66)
	Mean percent reduction in migraine day rate	Lewis, 2009[7]	-52.1 [58.6]	-73.3 [37.8]	21.20 (-1.90 to 44.30)	0.43 (-0.04 to 0.90)
	Last 4 week of double-phase: migraine attacks, number per month	Lewis, 2009[7]	1.9 [2.0]	1.1 [1.5]	0.80 (-0.02 to 1.62)	0.46 (-0.02 to 0.93)
	Mean percent reduction in migraine day rate	Lewis, 2009[7]	-52.5 [48.6]	-75.9 [32.4]	**23.40 (4.06 to 42.74)**	**0.57 (0.09 to 1.04)**
	Mean migraine time, days/month (last 4 weeks of double-blind phase)	Lewis, 2009[7]	2.8 [3.3]	2.0 [2.9]	0.80 (-0.65 to 2.25)	0.26 (-0.21 to 0.73)

Bold - significant difference at 95% confidence level

Appendix Table D41. Dose response effects with divalproex sodium in preventing migraine in children (results from low risk of bias randomized controlled clinical trial)[5]

Compared doses	Outcome	Events/ randomized with higher dose	Events/ randomized with lower dose	Relative risk (95% CI)	Absolute risk difference 95% CI)
Divalproex sodium 250mg vs. 500mg	≥50% reduction in 4 week migraine headache rate	33/83	27/74	1.1 (0.7 to 1.6)	0.03 (-0.12 to 0.18)
Divalproex sodium 250mg vs. 1000mg	≥50% reduction in 4 week migraine headache rate	33/83	37/75	0.8 (0.6 to 1.1)	-0.10 (-0.25 to 0.06)
Divalproex sodium 500mg vs. 1000mg	≥50% reduction in 4 week migraine headache rate	27/74	37/75	0.7 (0.5 to 1.1)	-0.13 (-0.29 to 0.03)

Appendix Table D42. Dose response reduction in migraine intermediate outcomes with divalproex sodium in children (results from randomized controlled clinical trials)

Compared doses	Outcome	Reference	Mean [Standard deviation] with higher dose	Mean [Standard deviation] with lower dose	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Divalproex sodium 250mg vs. 500mg	Migraine headache rate: Reduction from baseline, last 4 weeks	Apostol, 2008[5]	-1.7 [1.8]	-2.0 [1.8]	0.30 (-0.28 to 0.88)	0.16 (-0.15 to 0.48)
Divalproex sodium 250mg vs. 500mg	Migraine headache rate: experimental phase % reduction from baseline	Apostol, 2008[5]	-33.1 [56.2]	-36.3 [36.9]	3.20 (-11.52 to 17.92)	0.07 (-0.25 to 0.38)
Divalproex sodium 250mg vs. 500mg	4 week migraine headache days: experimental phase reduction from baseline	Apostol, 2008[5]	-2.8 [2.9]	-2.2 [3.2]	-0.60 (-1.56 to 0.36)	-0.20 (-0.51 to 0.12)
Divalproex sodium 250mg vs. 500mg	Percentage of migraine headaches treated with symptomatic medications: experimental phase reduction from baseline	Apostol, 2008[5]	-7.1 [34.0]	-8.0 [29.6]	0.90 (-9.04 to 10.84)	0.03 (-0.29 to 0.34)
Divalproex sodium 250mg vs. 1000mg	Migraine headache rate: reduction from baseline, last 4 weeks	Apostol, 2008[5]	-1.7 [1.8]	-1.8 [1.8]	0.10 (-0.46 to 0.66)	0.06 (-0.26 to 0.37)
Divalproex sodium 250mg vs. 1000mg	Migraine headache rate: experimental phase % reduction from baseline	Apostol, 2008[5]	-33.1 [56.2]	-39.6 [40.4]	6.50 (-8.65 to 21.65)	0.13 (-0.18 to 0.44)
Divalproex sodium 250mg vs. 1000mg	4-week migraine headache days: experimental phase reduction from baseline	Apostol, 2008[5]	-2.8 [2.9]	-3.1 [3.6]	0.30 (-0.73 to 1.33)	0.09 (-0.22 to 0.40)
Divalproex sodium 250mg vs. 1000mg	Percentage of migraine headaches treated with symptomatic medications: experimental phase reduction from baseline	Apostol, 2008[5]	-7.1 [34.0]	-8.5 [35.9]	1.40 (-9.52 to 12.32)	0.04 (-0.27 to 0.35)
Divalproex sodium 500mg vs. 1000mg	Migraine headache rate: reduction from baseline, last 4 weeks	Apostol, 2008[5]	2.0 [1.8]	1.8 [1.8]	0.20 (-0.38 to 0.78)	0.11 (-0.21 to 0.43)
Divalproex sodium 500mg vs. 1000mg	Migraine headache rate: experimental phase % reduction from baseline	Apostol, 2008[5]	36.3 [36.9]	39.6 [40.4]	-3.30 (-15.72 to 9.12)	-0.09 (-0.41 to 0.24)

Appendix Table D42. Dose response reduction in migraine intermediate outcomes with divalproex sodium in children (results from randomized controlled clinical trials) (continued)

Compared doses	Outcome	Reference	Mean [Standard deviation] with higher dose	Mean [Standard deviation] with lower dose	Mean difference (95% CI)	Cohen standardized mean difference (95% CI)
Divalproex sodium 500mg vs. 1000mg	4 week migraine headache days: experimental phase reduction from baseline	Apostol, 2008[5]	2.2 [3.2]	3.1 [3.6]	-0.90 (-1.99 to 0.19)	-0.26 (-0.59 to 0.06)
Divalproex sodium 500mg vs. 1000mg	Percentage of migraine headaches treated with symptomatic medications: experimental phase reduction from baseline	Apostol, 2008[5]	8.0 [29.6]	8.5 [35.9]	-0.50 (-11.05 to 10.05)	-0.02 (-0.34 to 0.31)
Divalproex Sodium Extended-release 250mg vs. 500mg	Reduction from baseline: 4 week migraine headache rate	Sheridan, 2008[6]	1.6 [1.7]	1.5 [1.6]	0.10 (-0.41 to 0.61)	0.06 (-0.25 to 0.37)
Divalproex Sodium Extended-release 250mg vs. 1000mg	Reduction from baseline: 4 week migraine headache rate	Sheridan, 2008[6]	1.6 [1.7]	1.5 [1.6]	0.10 (-0.41 to 0.61)	0.06 (-0.25 to 0.37)
Divalproex Sodium Extended-release 500mg vs. 1000mg	Reduction from baseline: 4 week migraine headache rate	Sheridan, 2008[6]	1.5 [1.6]	1.5 [1.6]	0.00 (-0.50 to 0.50)	0.00 (-0.32 to 0.32)

Appendix Table D43. Randomized controlled clinical trial that examined Internet-based self management for migraine prevention in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[20]

Reference Design Sample Number analyzed % females	Age	Definition of migraine	Presence of aura	Baseline subject characteristics	Duration of migraine	Prior treatment	Subject compliance and suitability
Trautmann, 2010[20] Design: RCT Sample: 68 Number analyzed: Not reported 54.55% females	Eligible age 10-18 years Mean age: 12.7 years	Not reported	Not reported	Headache diary: CBT: 11.5 (8.2), AR: 10.3 (7.8), Education: 10.7 (7.4), Intensity: CBT: 5.0 (1.8), AR: 5.1 (1.7), Education: 5.2 (1.70), Duration: CBT: 6.8 (4.0), AR: 8.1 (6.7), Education: 7.8 (5.8); KINDL-R: CBT: 3.6 (0.5), AR: 3.8 (0.6), Education: 3.8 (0.3); SDQ: CBT: 11.8 (3.5), AR: 8.9 (4.5), Education: 10.7 (3.9)	2.8 years	Not reported	Not reported

Appendix Table D44. Migraine prevention with Internet-based self management in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[20]

Active treatment	Control treatment	Definition of the outcome	Events/randomized with active Control treatments Rate of outcome in active [control group], %	Relative risk (95% CI)	Absolute risk difference (95% CI)
Self-help training program Multimodal cognitive-behavioral training (CBT) CBT was adapted from the face-to-face group therapy program devised by Denecke and Kroener-Herwig (2000) for children with recurrent headache. CBT was reduced from 8 to 6 sessions in a self-help format, and the protocol was adapted to adolescents up to 18 years. While the first module presented education on headaches, the second unit focused on stress management (perception of own stress symptoms, coping with stress). In the following modules the participants acquired progressive relaxation techniques, cognitive restructuring (identification of dysfunctional cognitions regarding headache and stress and identifying functional cognitions), self-assurance strategies (being proactive and sensitive to one's own needs), as well as problem solving. Participants of the CBT were offered a CD with relaxation instructions (a full relaxation protocol involving tensing and relaxing of major muscle groups, beginning with the upper body and proceeding to the lower body), and they could download the relaxation instructions from the training	Educational intervention Participants received only the first self-help module (education on headache), but they had the same number of e-mail contacts as those in the CBT and AR. The e-mails focused on the diary records of the previous week (e.g. Did you have any headache last week? What did you do?), rather than on cognitive-behavioral elements or applied relaxation instructions.	Subjective improvement of headache directly after training	12/24 9/19 50.0 [47.4]	1.1 (0.6 to 2.0)	0.03 (-0.27 to 0.33)

Appendix Table D44. Migraine prevention with Internet-based self management in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[19] (continued)

Active treatment	Control treatment	Definition of the outcome	Events/randomized with active Control treatments Rate of outcome in active [control group], %	Relative risk (95% CI)	Absolute risk difference (95% CI)
website. The participants responded to the assigned exercises and reported on their headache in the previous week through e-mail.					
Self-help training program Applied relaxation AR followed the training developed by O¨st (1987). The self-help modules contained only several phases from the original training (O¨ st, 1987): progressive relaxation, cue-controlled relaxation and differential relaxation. Participants were offered a CD with these specific instruction tracks for the different stages of AR training to be used at home (4 tracks: a full relaxation protocol common to the CBT CD, one track of cue-controlled relaxation, two tracks for differential relaxation). The participants responded to the assigned exercises and reported on their headache in the previous week through e-mail.	Educational intervention as above.	Subjective improvement of headache directly after training	12/22 9/19 54.5[47.4]	1.2 (0.6 to 2.1)	0.07 (-0.23 to 0.38)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	Subjective improvement of headache directly after training	12/24 12/22 50.0 [54.5]	0.9 (0.5 to 1.6)	-0.05 (-0.33 to 0.24)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	Responder (50% reduction in headache frequency) at 6 weeks	10/24 2/19 41.7 [10.5]	**4.0** **(1.0 to 16.0)**	**0.31** **(0.07 to 0.55)**
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	Responder (50% reduction in headache frequency) at 6 weeks	10/24 6/22 41.7 [27.3]	1.5 (0.7 to 3.5)	0.14 (-0.13 to 0.42)
Self-help training program Applied relaxation	Educational intervention	Responder (50% reduction in headache frequency) at 6 weeks	6/22 2/19 27.3 [10.5]	2.6 (0.6 to 11.4)	0.17 (-0.06 to 0.40)

Appendix Table D44. Migraine prevention with Internet-based self management in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[19] (continued)

Active treatment	Control treatment	Definition of the outcome	Events/randomized with active Control treatments Rate of outcome in active [control group], %	Relative risk (95% CI)	Absolute risk difference (95% CI)
Self-help training program Applied relaxation	Educational intervention	Responder (50% reduction in headache frequency) 6 months after completion of training	9/22 5/19 40.9 [26.3]	1.6 (0.6 to 3.8)	0.15 (-0.14 to 0.43)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	Responder (50% reduction in headache frequency) 6 months after completion of training	7/24 5/19 29.2 [26.3]	1.1 (0.4 to 2.9)	0.03 (-0.24 to 0.30)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	Responder (50% reduction in headache frequency) 6 months after completion of training	7/24 9/22 29.2 [40.9]	0.7 (0.3 to 1.6)	-0.12 (-0.39 to 0.16)

Bold - significant at 95% confidence level

Appendix Table D45. Migraine frequency with Internet-based self management for migraine prevention in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[20]

Active treatment	Control treatment	Definition of the outcome	Mean [STD] in active and control group	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
Self-help training program Applied relaxation	Educational intervention	Headache frequency : 6 weeks	7.4 [7.60] 6.7 [6.50]	0.70 (-3.62 to 5.02)	0.10 (-.52 to 0.71)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	Headache duration: 6 weeks	4.8 [2.90] 6.1 [5.10]	-1.30 (-3.87 to 1.27)	-0.32 (-.93 to 0.28)
Self-help training program Applied relaxation	Educational intervention	Headache duration: 6 weeks	6.2 [3.90] 6.1 [5.10]	0.10 (-2.71 to 2.91)	0.02 (-.59 to 0.64)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	Headache frequency: 6 weeks	4.9 [4.30] 7.4 [7.60]	-2.50 (-6.11 to 1.11)	-0.41 (-.99 to 0.18)
	Applied relaxation	Headache duration: 6 weeks	4.8 [2.90] 6.2 [3.90]	-1.40 (-3.40 to .60)	-0.41 (-.99 to 0.17)
	Educational intervention	Headache frequency: 6 weeks	4.9 [4.30] 6.7 [6.50]	-1.80 (-5.19 to 1.59)	-0.33 (-.94 to 0.27)
	Educational intervention	Headache intensity: 6 weeks	5.0 [2.40] 5.4 [2.00]	-0.40 (-1.72 to .92)	-0.18 (-.78 to 0.42)
Self-help training program Applied relaxation	Educational intervention	Headache intensity: 6 weeks	5.6 [1.90] 5.4 [2.00]	0.20 (-1.00 to 1.40)	0.10 (-.51 to 0.72)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	Headache intensity: 6 weeks	5.0 [2.40] 5.6 [1.90]	-0.60 (-1.85 to .65)	-0.28 (-.86 to 0.31)

Appendix Table D46. Quality of life with Internet-based self management for migraine prevention in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[20]

Active treatment	Control treatment	Definition of the outcome	Mean [STD] in active and control group	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	PCS-C (Pain Catastrophisizing Scale for Children: It is a self-report instrument on a 5-point rating scale): 6 weeks	27.1 [7.10] 31.7 [8.30]	-4.60 (-9.29 to 0.09)	-0.60 (-1.22 to 0.01)
Self-help training program Applied relaxation	Educational intervention	PCS-C (Pain Catastrophisizing Scale for Children: It is a self-report instrument on a 5-point rating scale): 6 weeks	34.7 [8.80] 31.7 [8.30]	3.00 (-2.24 to 8.24)	0.35 (-0.27 to 0.97)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	CDI at 6 weeks (Children's Depression Inventory: German version that includes 27 items measuring cognitive, affective, and behavioral symptoms of depression in childhood on a 3-point rating scale)	11.0 [9.20] 7.7 [5.20]	3.30 (-1.06 to 7.66)	0.43 (-0.18 to 1.04)
Self-help training program Applied relaxation	Educational intervention	CDI at 6 weeks (Children's Depression Inventory: German version that includes 27 items measuring cognitive, affective, and behavioral symptoms of depression in childhood on a 3-point rating scale)	8.1 [9.00] 7.7 [5.20]	0.40 (-4.03 to 4.83)	0.05 (-0.56 to 0.67)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	SDQ at 6 weeks (Strength and Difficulties Questionnaire: It is a brief questionnaire with five subscales for assessing relevant psychopathological symptoms in children and adolescents. It includes 25 items with a 5-point rating scale)	11.2 [4.30] 10.0 [4.90]	1.20 (-1.60 to 4.00)	0.26 (-0.34 to 0.87)

Appendix Table D46. Quality of life with Internet-based self management for migraine prevention in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[19] (continued)

Active treatment	Control treatment	Definition of the outcome	Mean [STD] in active and control group	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
Self-help training program Applied relaxation	Educational intervention	SDQ at 6 weeks (Strength and Difficulties Questionnaire: It is a brief questionnaire with five subscales for assessing relevant psychopathological symptoms in children and adolescents. It includes 25 items with a 5-point rating scale)	9.5 [4.20] 10.0 [4.90]	-0.50 (-3.32 to 2.32)	-0.11 (-0.72 to 0.50)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Educational intervention	KINDL-R at 6 weeks (German KINDL - questionnaire (Ravens-Sieberer & Bullinger, 1998) that includes six dimensions of health-related quality of life)	3.6 [0.40] 3.9 [0.30]	-0.30 (-0.51 to -0.09)	-0.83 (-1.46 to -0.21)
Self-help training program Applied relaxation	Educational intervention	KINDL-R at 6 weeks (German KINDL - questionnaire (Ravens-Sieberer & Bullinger, 1998) that includes six dimensions of health-related quality of life)	3.8 [0.60] 3.9 [0.30]	-0.10 (-0.38 to 0.18)	-0.21 (-0.82 to 0.41)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	PCS-C (Pain Catastrophisizing Scale for Children: It is a self-report instrument on a 5-point rating scale): 6 weeks	27.1 [7.10] 34.7 [8.80]	-7.60 (-12.25 to -2.95)	-0.96 (-1.57 to -0.34)
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation	CDI at 6 weeks (Children's Depression Inventory: German version that includes 27 items measuring cognitive, affective, and behavioral symptoms of depression in childhood on a 3-point rating scale)	11.0 [9.20] 8.1 [9.00]	2.90 (-2.36 to 8.16)	0.32 (-0.26 to 0.90)
Self-help training program Multimodal cognitive-behavioral	Applied relaxation	SDQ at 6 weeks (Strength and Difficulties	11.2 [4.30] 9.5 [4.20]	1.70 (-0.76 to 4.16)	0.40 (-0.18 to 0.98)

Appendix Table D46. Quality of life with Internet-based self management for migraine prevention in childhood and adolescence (unclear risk of bias randomized controlled clinical trial)[19] (continued)

Active treatment	Control treatment	Definition of the outcome	Mean [STD] in active and control group	Mean difference (95% CI)	Standardized Cohen mean difference (95% CI)
training (CBT)		Questionnaire: It is a brief questionnaire with five subscales for assessing relevant psychopathological symptoms in children and adolescents. It includes 25 items with a 5-point rating scale)			
Self-help training program Multimodal cognitive-behavioral training (CBT)	Applied relaxation assigned exercises and reported on their headache in the previous week through e-mail.	KINDL-R at 6 weeks (German KINDL - questionnaire (Ravens-Sieberer & Bullinger, 1998) that includes six dimensions of health-related quality of life)	3.6 [0.40] 3.8 [0.60]	-0.20 (-0.50 to 0.10)	-0.40 (-0.98 to 0.19)

Appendix Table D47. Randomized controlled clinical trials that examined adverse effects of preventive drugs in children with migraine

Reference, Sample, Number analyzed, % female	Drug	Age	Definition of migraine	Presence of aura	Migraine duration and baseline severity	Comorbidity	Concurrent medication	Duration of migraine	Subject compliance and suitability
Battistella, 1993[4] Sample: 40 Number analyzed: Not reported 45% female	Trazodone	Eligible age 7 to 18 years Mean 12.6 years	International Headache Society criteria for migraine	All patients had migraine without aura (inclusion criterion)	History of symptoms (years), mean (SD): 4.5 (1.3); mean frequency of attacks/month: Trazodone: 4.0±0.2 and Placebo: 3.5±0.1; Mean duration of attacks in hours: Trazodone: 20.2±1.3 and Placebo: 18.2±1.1	Not reported	Not reported	4.5 years	Not reported
Wang, 2003[21] Sample: 118 Number analyzed: 118 68.6% female	Oral magnesium oxide	Eligible age Between 3 and 17 Mean 12.0 years	History of at least weekly, moderate-to-severe migraine during the previous 4 weeks and it must have been associated with anorexia/ nausea, vomiting, photophobia, sonophobia, a pulsatile or throbbing quality, or relief with sleep, but not with fever or evidence of infection.	Not reported	Headaches in last month, mean (SD) [median]: magnesium oxide: 9.3 (4.7) [8] and placebo: 11.5 (8.1) [8]	15.4% had asthma, 17% had allergies; 8.5% had depression	Patients were excluded if they took any migraine prophylactic drug therapies (such as beta-blockers, valproic acid), mg, or fever medications within 4 weeks of potential study entrance.	Age at first headache: 8.5 years	Compliance was assessed through the use of capsule counts, which were performed at week 4 and again at study's end

Appendix Table D47. Randomized controlled clinical trials that examined adverse effects of preventive drugs in children with migraine (continued)

Reference, Sample, Number analyzed, % female	Drug	Age	Definition of migraine	Presence of aura	Migraine duration and baseline severity	Comorbidity	Concurrent medication	Duration of migraine	Subject compliance and suitability
Winner, 2005[8] Sample: 162 Number analyzed: 157 48.4% female	Topiramate	Eligible age 6 to 15 years Mean 11.1 years	According to International Headache Society classification of pediatric migraine with or without aura	Not reported	Mean (SD) monthly migraine days: topiramate: 5.4 (1.7) and placebo: 5.5 (2.0)	Not reported	Not reported	Not reported	Not reported
Winner, 2006[17] Sample: 51 Number analyzed: 49 71% female	Topiramate	Eligible age 12 to 17 years Mean 14 years	International Headache Society criteria	Not reported	Migraine frequency, Mean (SD): Placebo: 4.6 (2.1), Topiramate 50mg/day: 4.8 (1.9), Topiramate 100mg/day: 6.2 (3.5), Topiramate 200mg/day: 4.9 (2.0)	Not reported	Prophylactic medications were not permitted	Not reported	Not reported
Apostol, 2008[5] Sample: 305 Number analyzed: 299 55% female	Divalproex sodium extended-release	Eligible age 12 to 17 years Mean 14.2 years	IHS criteria	Not reported	Migraine headaches within 3 months prior to screening: Mean (SD): Placebo: 16.7 (7.62), 250 mg DVPX ER: 16.6 (7.02), 500 mg DVPX ER: 18.0 (7.02), 1000 mg DVPX ER:17.3 (6.84)	Not reported	Prophylactic medications were not permitted	Not reported	To document compliance with study medication, subjects were instructed to return all medication bottles and pill counts were performed. Site personnel were to counsel any subject with compliance <70%.
Lewis, 2009[7] Sample: 106	Topiramate	Eligible age	International Headache	Not reported	Mean migraine attacks, no/month:	Not reported	Not reported	Not reported	Subjects maintained

Appendix Table D47. Randomized controlled clinical trials that examined adverse effects of preventive drugs in children with migraine (continued)

Reference, Sample, Number analyzed, % female	Drug	Age	Definition of migraine	Presence of aura	Migraine duration and baseline severity	Comorbidity	Concurrent medication	Duration of migraine	Subject compliance and suitability
Number analyzed: 103 61% female		between 12 and 17 years Mean 14.2 years	Society guidelines for pediatric migraine		placebo: 4.1±1.48; 50mg topiramate: 4.1±1.74 and 100mg topiramate: 4.3±1.59				medication records the accuracy of which was checked by their parents.
Pandina, 2010[19] Sample: 103 Number analyzed: 103 61% female	Topiramate	Eligible age 12 to 17 years Mean: 14.2 years	International Headache Society criteria for pediatric migraine	Not reported	Not reported	Not reported	88.3% of subjects reported concomitant use of acute headache medications for migraine.	Not reported	Not reported
Sillanpää, 1977[2] Sample: 57 Number analyzed: 57 38.6% female	Clonidine	Eligible age 0-15 years Mean 11 years	Migraine was defined by the criteria of Vahlquist, i.e. paroxysmal headache separated by headache-free intervals and at least two of the following four: unilateral pain, nausea, visual aura and positive family history.	12 patients in the clonidine group and 8 patients in the placebo group had classic migraine with visual aura.	Frequency of headache/month (n): 5-6: Clonidine: 3 and Placebo: 4, and >6: Clonidine: 5 and Placebo: 6	Not reported	Not reported	Not reported	Not reported
Freitag, 2003[22] Sample: 53 Number analyzed: 39 46.2% female	Propranolol	Eligible age 9 to 15 years Mean age not reported	Migraine was defined as a periodic headache with at least three of four feature: aura,	Not reported	Frequency of attacks: 2-5/week: Propranolol: 12 and Placebo: 4;	Not reported	Not reported	Age at first attack (no.): 3-5 years: Propranolol: 3, 6-10 years: 13 and 11-12	As a measure of compliance, the number of tablets remaining from the

Appendix Table D47. Randomized controlled clinical trials that examined adverse effects of preventive drugs in children with migraine (continued)

Reference, Sample, Number analyzed, % female	Drug	Age	Definition of migraine	Presence of aura	Migraine duration and baseline severity	Comorbidity	Concurrent medication	Duration of migraine	Subject compliance and suitability
			nausea, vomiting, and positive family history					years: 6 and Placebo: 3-5 years: 5, 6-10 years: 11 and 11-12 years: 1	dispensed was recorded
Sheridan, 2008[6] Sample: 305 Number analyzed: 299 % females Not reported	Depakote ER	Eligible age 12 to 17 years Mean age not reported	International Headache Society criteria for migraine	Not reported	Mean (SD): Migraine headache rate: Divalproex sodium 250mg: 4.0 (1.27); Divalproex sodium 500mg: 3.9 (1.28), Divalproex sodium 1000mg: 3.6 (1.08), Placebo: 4.0 (1.31)	Not reported	Not reported	Not reported	Not reported

Appendix Table D48. Adverse effects with migraine preventive drugs in children (results from nonrandomized studies)

Reference Design of study	Migraine definition Age	Drug Daily dose	Adverse effect	Events/treated Treatment weeks	Rate of outcome,%
Lewis, 2004[23] Retrospective review	International Classification of Diseases [ICD] code 884.0 and ICD codes 346.0, 346.1 and 346.2 Age <18	Amitriptyline Not reported	Discontinued treatment	2/73 Treatment weeks not reported	2.7
Apostol, 2009[24] Open-label clinical trial	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Any adverse event	203/241 Treatment weeks 48	84.2
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Nausea	45/241 Treatment weeks 48	18.7
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Vomiting	43/241 Treatment weeks 48	17.8
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Weight gain	29/241 Treatment weeks 48	12.0
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Nasopharyngitis	27/241 Treatment weeks 48	11.2
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Migraine	25/241 Treatment weeks 48	10.4
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Upper respiratory tract infection	25/241 Treatment weeks 48	10.4
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	One or more serious adverse effects	10/241 Treatment weeks 48	4.1
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Irregular menses	2/241 Treatment weeks 48	0.8
Pakalnis, 2001[25] Retrospective review	International Headache Society criteria Age <17	Divalproex 250mg to 1125mg/day (3.1-32.9mg/kg/day)	Discontinued due to side effects	4/23 Treatment weeks not reported	17.4
	International Headache Society criteria Age <17	Divalproex 250mg to 1125mg/day (3.1-32.9mg/kg/day)	Discontinued due to weight gain	1/23 Treatment weeks not reported	4.3
	International Headache	Divalproex	Discontinued due to lethargy	1/23	4.3

Appendix Table D48. Adverse effects with migraine preventive drugs in children (results from nonrandomized studies) (continued)

Reference Design of study	Migraine definition Age	Drug Daily dose	Adverse effect	Events/treated Treatment weeks	Rate of outcome,%
	Society criteria Age <17	250mg to 1125mg/day (3.1-32.9mg/kg/day)		Treatment weeks not reported	
	International Headache Society criteria Age <17	Divalproex 250mg to 1125mg/day (3.1-32.9mg/kg/day)	Discontinued due to anorexia	1/23 Treatment weeks not reported	4.3
	International Headache Society criteria Age <17	Divalproex 250mg to 1125mg/day (3.1-32.9mg/kg/day)	Discontinued due to alopecia	1/23 Treatment weeks not reported	4.3
Apostol, 2009[24] Open-label clinical trial	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Weight gain leading to discontinuation	6/241 Treatment weeks 48	2.5
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Alopecia leading to discontinuation	5/241 Treatment weeks 48	2.1
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Nausea leading to discontinuation	4/241 Treatment weeks 48	1.7
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Increased ammonia leading to discontinuation	3/241 Treatment weeks 48	1.2
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Migraine leading to discontinuation	3/241 Treatment weeks 48	1.2
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Upper abdominal pain leading to discontinuation	2/241 Treatment weeks 48	0.8
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Depressed mood leading to discontinuation	2/241 Treatment weeks 48	0.8
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Depression leading to discontinuation	2/241 Treatment weeks 48	0.8
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Irritability leading to discontinuation	2/241 Treatment weeks 48	0.8
	International Headache Society criteria Age 12 to 17 years	Divalproex 250 to 1000mg/day	Psychiatric adverse effects	4/241 Treatment weeks 48	1.7
Pakalnis, 2007[26] Prospective	ICHD-II Age 6 to 17 years	Levetiracetam 20mg/kg/day	Behavioral changes (irritability and aggressiveness)	2/22 Treatment weeks 16	9.1
	ICHD-II Age 6 to 17 years	Levetiracetam 20mg/kg/day	Mild memory problems	1/22 Treatment weeks 16	4.5

Appendix Table D48. Adverse effects with migraine preventive drugs in children (results from nonrandomized studies) (continued)

Reference Design of study	Migraine definition Age	Drug Daily dose	Adverse effect	Events/treated Treatment weeks	Rate of outcome,%
Miller, 2004[27] Retrospective review	International Headache Society criteria Age <17	Levetiracetam 125 or 250mg twice daily	Irritability and moodiness attenuated after 1 month of treatment	1/23 Treatment weeks 4	4.3
	International Headache Society criteria Age <17	Levetiracetam 125 or 250mg twice daily	Discontinued due to side effects	2/23 Treatment weeks not reported	8.7
	International Headache Society criteria Age <17	Levetiracetam 125 or 250mg twice daily	Discontinued due to asthenia/ somnolence and dizziness	1/23 Treatment weeks not reported	4.3
	International Headache Society criteria Age <17	Levetiracetam 125 or 250mg twice daily	Discontinued due to irritability, hyperactivity, and hostile behavior	1/23 Treatment weeks not reported	4.3
Cruz, 2009[28] Retrospective review	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Cognitive decline	5/37 Treatment weeks not reported	13.5
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Drowsiness	3/37 Treatment weeks not reported	8.1
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Paresthesia	1/37 Treatment weeks not reported	2.7
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Anhidrosis	1/37 treatment weeks not reported	2.7
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Discontinued due to adverse effects	7/37 Treatment weeks not reported	18.9
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Discontinued due to cognitive issues	5/37 Treatment weeks not reported	13.5
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Discontinued due to paresthesia	1/37 Treatment weeks not reported	2.7
	International Headache Society criteria (2004) Age <21	Topiramate 50 to 200mg/day	Discontinued due to anhidrosis	1/37 t Treatment weeks not reported	2.7
Jurgens, 2011[29] Case report	Not reported Age 17 year old	Topiramate 25mg initial dose then increased gradually to 75mg/day	"Alice in Wonderland syndrome" (on 75mg/day dose and not on lower doses): Intermittent nocturnal distortions of her body image only on occasions when she did not directly fall asleep	0/1 Treatment weeks 16	

Appendix Table D48. Adverse effects with migraine preventive drugs in children (results from nonrandomized studies) (continued)

Reference Design of study	Migraine definition Age	Drug Daily dose	Adverse effect	Events/treated Treatment weeks	Rate of outcome,%
			after taking topiramate. Her head would grow bigger and the rest of the body would shrink, or that her hand resting comfortably on her chest would increase in size and become heavier, while the remaining arm would become smaller.		
Taylor, 2007[30] Retrospective and concurrent chart review	Not reported Age <18	Valproic acid Loading dose of 20-40mg/kg over one hour followed by a continuous intravenous infusion at 1-1.5mg/kg/hour	Hyperammonemia	1/26 Treatment weeks 12	3.8
	Not reported Age <18	Valproic acid Loading dose of 20-40mg/kg over one hour followed by a continuous intravenous infusion at 1-1.5mg/kg/hour	Hallucinations	1/26 Treatment weeks not reported	3.8
	Not reported Age <18	Valproic acid Loading dose of 20-40mg/kg over one hour followed by a continuous intravenous infusion at 1-1.5mg/kg/hour	Confusion (during the initial loading phase)	1/26 Treatment weeks not reported	3.8
Chan, 2009[31] Prospective	Not reported Age 14-18 years	Botox 100U every 3 months (follow-the pain approach)	Mild ptosis	1/12 Treatment weeks 12	8.3
	Not reported Age 14-18 years	Botox 100U every 3 months (follow-the pain approach)	Blurred vision	1/12 Treatment weeks 12	8.3
	Not reported Age 14-18 years	Botox 100U every 3 months (follow-the pain approach)	Hematoma at one of neck injection site with resultant tingling in one arm lasting 24 hours	1/12 Treatment weeks not reported	8.3
	Not reported Age 14-18 years	Botox 100U every 3 months (follow-the pain approach)	Burning sensations at all injection sites lasting 1 week	1/12 Treatment weeks 116	8.3

Appendix Table D49. Treatment discontinuation due to adverse effects with topiramate for migraine prevention in children (pooled with random effects model results from randomized controlled clinical trials)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Treatment discontinuation	100mg	Pandina, 2010[19] Low	5/35 [14.3]	7/33 [21.2]	0.7 (0.2 to 1.9)	11.65	-0.07 (-0.25 to 0.11)	14.9
Treatment discontinuation	100mg	Winner, 2006[17] Low	3/13 [23.1]	5/12 [41.7]	0.6 (0.2 to 1.8)	8.87	-0.19 (-0.55 to 0.18)	3.76
Treatment discontinuation	100mg	Lewis, 2009[7] Low	6/35 [17.1]	7/33 [21.2]	0.8 (0.3 to 2.2)	13.2	-0.04 (-0.23 to 0.15)	13.99
Treatment discontinuation	100mg	Pooled	14/83 [16.9]	19/78 [24.4]	0.7 (0.4 to 1.3)	33.71	-0.07 (-0.19 to 0.05)	32.65
Treatment discontinuation	200mg	Winner, 2006[17] Low	2/14 [14.3]	5/12 [41.7]	0.3 (0.1 to 1.5)	6.07	-0.27 (-0.61 to 0.06)	4.4
Treatment discontinuation	200mg	Lewis, 2009[7] Low	5/35 [14.3]	7/33 [21.2]	0.7 (0.2 to 1.9)	11.65	-0.07 (-0.25 to 0.11)	14.9
Treatment discontinuation	200mg	Winner, 2005[8] Moderate	23/112 [20.5]	8/50 [16.0]	1.3 (0.6 to 2.7)	23.7	0.05 (-0.08 to 0.17)	30.78
Treatment discontinuation	200mg	Pooled	30/161 [18.6]	20/95 [21.1]	0.8 (0.4 to 1.6)	41.42	-0.05 (-0.19 to 0.10)	50.08
Treatment discontinuation	50mg	Pandina, 2010[19] Low	6/35 [17.1]	7/33 [21.2]	0.8 (0.3 to 2.2)	13.2	-0.04 (-0.23 to 0.15)	13.99
Treatment discontinuation	50mg	Winner, 2006[17] Low	4/12 [33.3]	5/12 [41.7]	0.8 (0.3 to 2.3)	11.67	-0.08 (-0.47 to 0.30)	3.29
Treatment discontinuation	50mg	Pooled	10/47 [21.3]	12/45 [26.7]	0.8 (0.4 to 1.6)	24.87	-0.05 (-0.22 to 0.12)	17.28
Treatment discontinuation	Overall	Pooled	54/291 [18.6]	51/218 [23.4]	0.8 (0.6 to 1.1)	100	-0.04 (-0.11 to 0.03)	100
Treatment discontinuation due to adverse events	100mg	Pandina, 2010[19] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	25	0.06 (-0.05 to 0.17)	25
Treatment discontinuation due to adverse events	100mg	Lewis, 2009[7] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	25	0.06 (-0.05 to 0.17)	25
Treatment discontinuation	100mg	Pooled	6/70 [8.6]	2/66 [3.0]	2.8 (0.6 to 13.5)	50	0.06 (-0.02 to 0.13)	50

Appendix Table D49. Treatment discontinuation due to adverse effects with topiramate for migraine prevention in children (pooled with random effects model results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
due to adverse events								
Treatment discontinuation due to adverse events	200mg	Lewis, 2009[7] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	25	0.06 (-0.05 to 0.17)	25
Treatment discontinuation due to adverse events	50mg	Pandina, 2010[19] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	25	0.06 (-0.05 to 0.17)	25
Treatment discontinuation due to adverse events	Overall	Pooled	12/140 [8.6]	4/132 [3.0]	2.8 (0.9 to 8.6)	100	**0.06 (0.00 to 0.11)**	100

Appendix Table D50. Strength of evidence about treatment discontinuation due to adverse effects with antiepileptic drugs for migraine prevention in children

Active drug	Dose	Rate with drug [placebo]	RCTs	Children	Directness	Risk of bias	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Divalproex sodium	1000mg	9.3 [1.4]	2	296	Yes	Low	Yes	No	Yes	Low	Divalproex sodium 1000mg resulted in greater treatment discontinuation rates vs. placebo
	250mg	2.4 [1.4]	2	312	Yes	Low	Yes	No	Yes	Low	Divalproex sodium 250mg did not result in greater treatment discontinuation rates vs. placebo
	Overall	4.6 [1.4]	2	755	Yes	Low	Yes	No	Yes	Low	Divalproex sodium resulted in greater treatment discontinuation rates vs. placebo
Topiramate	100mg	8.6 [3]	2	136	Yes	Low	Yes	No	No	Low	Topiramate 100mg did not result in greater treatment discontinuation rates vs. placebo
	Overall	8.6 [3]	2	272	Yes	Low	Yes	No	No	Low	Topiramate resulted in greater treatment discontinuation rates vs. placebo

Appendix Table D51. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials)

Outcome	Reference Risk of bias	Dose	Events/randomized [rate] with drug	Events/randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abnormal vision	Lewis, 2009[7] Low	100mg	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	0.00 (-0.08 to 0.08)
	Lewis, 2009[7] Low	200mg	2/35 [5.7]	1/33 [3.0]	1.9 (0.2 to 19.8)	0.03 (-0.07 to 0.12)
Allergy	Lewis, 2009[7] Low	200mg	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	0.06 (-0.04 to 0.15)
Any adverse event	Winner, 2006[17] Low	100mg	11/13 [84.6]	10/12 [83.3]	1.0 (0.7 to 1.4)	0.01 (-0.28 to 0.30)
	Winner, 2006[17] Risk of bias Low	200mg	12/14 [85.7]	10/12 [83.3]	1.0 (0.7 to 1.4)	0.02 (-0.26 to 0.30)
	Winner, 2006[17] Low	50mg	8/12 [66.7]	10/12 [83.3]	0.8 (0.5 to 1.3)	-0.17 (-0.51 to 0.17)
Any treatment related adverse event	**Lewis, 2009[7] Risk of bias Low**	**100mg**	**26/35 [74.3]**	**16/33 [48.5]**	**1.5 (1.0 to 2.3)**	**0.26 (0.03 to 0.48)**
	Lewis, 2009[7] Low	**200mg**	**26/35 [74.3]**	**16/33 [48.5]**	**1.5 (1.0 to 2.3)**	**0.26 (0.03 to 0.48)**
Asthma	Lewis, 2009[7] Low	200mg	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	0.06 (-0.04 to 0.15)
Back pain	Lewis, 2009[7] Low	100mg	0/35 [0.0]	3/33 [9.1]	0.1 (0.0 to 2.5)	-0.09 (-0.20 to 0.02)
	Lewis, 2009[7] Low	200mg	2/35 [5.7]	3/33 [9.1]	0.6 (0.1 to 3.5)	-0.03 (-0.16 to 0.09)
Bronchitis	Winner, 2006[17] Low	100mg	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	-0.01 (-0.22 to 0.21)
	Winner, 2006[17] Low	200mg	0/14 [0.0]	1/12 [8.3]	0.3 (0.0 to 6.5)	-0.08 (-0.28 to 0.11)
	Winner, 2006[17] Risk of bias Low	50mg	0/12 [0.0]	1/12 [8.3]	0.3 (0.0 to 7.5)	-0.08 (-0.29 to 0.12)
Conjunctivitis	Lewis, 2009[7] Low	100mg	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	0.06 (-0.05 to 0.17)
	Lewis, 2009[7] Low	200mg	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	0.00 (-0.08 to 0.08)
Cough	Lewis, 2009[7] Risk of bias Low	100mg	3/35 [8.6]	0/33 [0.0]	6.6 (0.4 to 123.3)	0.09 (-0.02 to 0.19)
	Lewis, 2009[7] Low	200mg	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	0.03 (-0.05 to 0.11)
Depression	Pandina, 2010[19] Risk of bias Low	50mg	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	0.03 (-0.05 to 0.11)

Appendix Table D51. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Reference Risk of bias	Dose	Events/randomized [rate] with drug	Events/randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Diarrhea	Winner, 2006[17] Low	100mg	1/13 [7.7]	0/12 [0.0]	2.8 (0.1 to 62.5)	0.08 (-0.12 to 0.27)
	Winner, 2006[17] Risk of bias Low	200mg	1/14 [7.1]	0/12 [0.0]	2.6 (0.1 to 58.5)	0.07 (-0.11 to 0.26)
Difficulty concentration/attention	Pandina, 2010[19] Risk of bias Low	100mg	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	0.03 (-0.05 to 0.11)
	Winner, 2006[17] Low	200mg	2/14 [14.3]	0/12 [0.0]	4.3 (0.2 to 82.3)	0.14 (-0.07 to 0.36)
Difficulty memory numbers	Winner, 2006[17] Low	100mg	0/13 [0.0]	1/12 [8.3]	0.3 (0.0 to 6.9)	-0.08 (-0.28 to 0.12)
	Winner, 2006[17] Low	200mg	1/14 [7.1]	1/12 [8.3]	0.9 (0.1 to 12.3)	-0.01 (-0.22 to 0.19)
	Winner, 2006[17] Low	50mg	0/12 [0.0]	1/12 [8.3]	0.3 (0.0 to 7.5)	-0.08 (-0.29 to 0.12)
Emotional stress	Pandina, 2010[19] Low	50mg	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	0.03 (-0.05 to 0.11)
Eye pain	Lewis, 2009[7] Low	100mg	1/35 [2.9]	2/33 [6.1]	0.5 (0.0 to 5.0)	-0.03 (-0.13 to 0.07)
	Lewis, 2009[7] Low	200mg	1/35 [2.9]	2/33 [6.1]	0.5 (0.0 to 5.0)	-0.03 (-0.13 to 0.07)
Fever	Lewis, 2009[7] Low	100mg	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	0.06 (-0.04 to 0.15)
	Winner, 2005[8] Moderate	200mg	6/112 [5.4]	2/50 [4.0]	1.3 (0.3 to 6.4)	0.01 (-0.05 to 0.08)
	Lewis, 2009[7] Low	200mg	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	0.06 (-0.04 to 0.15)
Gastroenteritis	Winner, 2005[8] Moderate	200mg	10/112 [8.9]	3/50 [6.0]	1.5 (0.4 to 5.2)	0.03 (-0.06 to 0.11)
Infection, viral	Winner, 2006[17] Low	100mg	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	-0.01 (-0.22 to 0.21)
	Winner, 2006[17] Low	200mg	2/14 [14.3]	1/12 [8.3]	1.7 (0.2 to 16.6)	0.06 (-0.18 to 0.30)
	Winner, 2006[17] Low	50mg	1/12 [8.3]	1/12 [8.3]	1.0 (0.1 to 14.2)	0.00 (-0.22 to 0.22)
Influenza-like symptoms	Winner, 2005[8] Moderate	200mg	8/112 [7.1]	2/50 [4.0]	1.8 (0.4 to 8.1)	0.03 (-0.04 to 0.10)
Language problems	Winner, 2006[17] Low	100mg	0/13 [0.0]	1/12 [8.3]	0.3 (0.0 to 6.9)	-0.08 (-0.28 to 0.12)
	Winner, 2006[17]	200mg	2/14	1/12	1.7 (0.2 to 16.6)	0.06 (-0.18 to 0.30)

Appendix Table D51. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Reference Risk of bias	Dose	Events/randomized [rate] with drug	Events/randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
	Low		[14.3]	[8.3]		
	Winner, 2006[17] Low	50mg	0/12 [0.0]	1/12 [8.3]	0.3 (0.0 to 7.5)	-0.08 (-0.29 to 0.12)
Pneumonia	Lewis, 2009[7] Low	200mg	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	0.06 (-0.04 to 0.15)
Psychomotor slowing	Winner, 2006[17] Low	200mg	1/14 [7.1]	0/12 [0.0]	2.6 (0.1 to 58.5)	0.07 (-0.11 to 0.26)
	Winner, 2006[17] Low	50mg	1/12 [8.3]	0/12 [0.0]	3.0 (0.1 to 67.1)	0.08 (-0.12 to 0.29)
Taste perversion	Lewis, 2009[7] Low	100mg	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	0.03 (-0.05 to 0.11)
	Lewis, 2009[7] Low	200mg	3/35 [8.6]	0/33 [0.0]	6.6 (0.4 to 123.3)	0.09 (-0.02 to 0.19)
Viral infection	Lewis, 2009[7] Low	100mg	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	0.00 (-0.08 to 0.08)
	Lewis, 2009[7] Low	200mg	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	0.06 (-0.05 to 0.17)
Vomiting	Lewis, 2009[7] Low	100mg	0/35 [0.0]	1/33 [3.0]	0.3 (0.0 to 7.5)	-0.03 (-0.11 to 0.05)
	Lewis, 2009[7] Low	200mg	2/35 [5.7]	1/33 [3.0]	1.9 (0.2 to 19.8)	0.03 (-0.07 to 0.12)

Appendix Table D52. Adverse effects with topiramate versus placebo in children (pooled with random effects results from randomized controlled clinical trials)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Abdominal pain	100mg	Winner, 2006[17] Low	2/13 [15.4]	1/12 [8.3]	1.8 (0.2 to 17.8)	7.45	0.07 (-0.18 to 0.32)	6.48
Abdominal pain	100mg	Lewis, 2009[7] Low	3/35 [8.6]	3/33 [9.1]	0.9 (0.2 to 4.3)	16.43	-0.01 (-0.14 to 0.13)	22.37
Abdominal pain	100mg	Pooled	5/48 [10.4]	4/45 [8.9]	1.2 (0.3 to 4.1)	23.88	0.01 (-0.11 to 0.13)	28.84
Abdominal pain	200mg	Winner, 2006[17] Low	2/14 [14.3]	1/12 [8.3]	1.7 (0.2 to 16.6)	7.42	0.06 (-0.18 to 0.30)	7.02
Abdominal pain	200mg	Lewis, 2009[7] Low	5/35 [14.3]	3/33 [9.1]	1.6 (0.4 to 6.1)	21.05	0.05 (-0.10 to 0.20)	17.67
Abdominal pain	200mg	Winner, 2005[8] Moderate	11/112 [9.8]	6/50 [12.0]	0.8 (0.3 to 2.1)	43.67	-0.02 (-0.13 to 0.08)	36.55
Abdominal pain	200mg	Pooled	18/161 [11.2]	10/95 [10.5]	1.1 (0.5 to 2.2)	72.14	0.01 (-0.07 to 0.09)	61.24
Abdominal pain	50mg	Winner, 2006[17] Low	0/12 [0.0]	1/12 [8.3]	0.3 (0.0 to 7.5)	3.97	-0.08 (-0.29 to 0.12)	9.92
Abdominal pain	Overall	Pooled	23/221 [10.4]	15/152 [9.9]	1.0 (0.6 to 1.9)	100	0.00 (-0.06 to 0.06)	100
Anorexia	100mg	Pandina, 2010[19] Low	4/35 [11.4]	1/33 [3.0]	3.8 (0.4 to 32.0)	9.81	0.08 (-0.04 to 0.21)	14.72
Anorexia	100mg	Winner, 2006[17] Low	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	6.35	-0.01 (-0.22 to 0.21)	4.71
Anorexia	100mg	Lewis, 2009[7] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	9.17	0.06 (-0.05 to 0.17)	17.79
Anorexia	100mg	Pooled	8/83 [9.6]	3/78 [3.8]	2.4 (0.6 to 9.0)	25.34	0.06 (-0.02 to 0.14)	37.22
Anorexia	200mg	Winner, 2006[17] Low	2/14 [14.3]	1/12 [8.3]	1.7 (0.2 to 16.6)	8.69	0.06 (-0.18 to 0.30)	3.68
Anorexia	200mg	Lewis, 2009[7] Low	4/35 [11.4]	1/33 [3.0]	3.8 (0.4 to 32.0)	9.81	0.08 (-0.04 to 0.21)	14.72
Anorexia	200mg	Winner, 2005[8] Moderate	15/112 [13.4]	4/50 [8.0]	1.7 (0.6 to 4.8)	40.62	0.05 (-0.04 to 0.15)	22.21
Anorexia	200mg	Pooled	21/161 [13.0]	6/95 [6.3]	1.9 (0.8 to 4.6)	59.12	0.07 (-0.01 to 0.14)	40.61
Anorexia	50mg	Pandina, 2010[19] C Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	9.17	0.06 (-0.05 to 0.17)	17.79

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Anorexia	50mg	Winner, 2006[17] Risk of bias Low	1/12 [8.3]	1/12 [8.3]	1.0 (0.1 to 14.2)	6.38	0.00 (-0.22 to 0.22)	4.37
Anorexia	50mg	Pooled	4/47 [8.5]	2/45 [4.4]	1.8 (0.3 to 10.1)	15.55	0.04 (-0.05 to 0.14)	22.17
Anorexia	**Overall**	**Pooled**	**33/291 [11.3]**	**11/218 [5.0]**	**2.0 (1.0 to 3.9)**	**100**	**0.06 (0.01 to 0.11)**	**100**
Dizziness	100mg	Pandina, 2010[19] Low	3/35 [8.6]	0/33 [0.0]	6.6 (0.4 to 123.3)	14.41	0.09 (-0.02 to 0.19)	18.72
Dizziness	100mg	Winner, 2006[17] Low	0/13 [0.0]	2/12 [16.7]	0.2 (0.0 to 3.5)	14.35	-0.17 (-0.40 to 0.07)	6.42
Dizziness	100mg	Lewis, 2009[7] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	14.11	0.06 (-0.04 to 0.15)	20.95
Dizziness	100mg	Pooled	5/83 [6.0]	2/78 [2.6]	1.8 (0.2 to 16.8)	42.86	0.04 (-0.06 to 0.14)	46.1
Dizziness	200mg	Winner, 2006[17] Low	0/14 [0.0]	2/12 [16.7]	0.2 (0.0 to 3.3)	14.33	-0.17 (-0.40 to 0.07)	6.54
Dizziness	200mg	Lewis, 2009[7] Low	3/35 [8.6]	0/353 [0.0]	68.8 (3.6 to 1306.3)	14.34	0.09 (-0.01 to 0.18)	20.13
Dizziness	200mg	Pooled	3/49 [6.1]	2/365 [0.5]	3.5 (0.0 to 1217.0)	28.67	-0.02 (-0.26 to 0.23)	26.67
Dizziness	50mg	Pandina, 2010[19] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	14.11	0.06 (-0.04 to 0.15)	20.95
Dizziness	50mg	Winner, 2006[17] Low	0/12 [0.0]	2/12 [16.7]	0.2 (0.0 to 3.8)	14.36	-0.17 (-0.41 to 0.07)	6.28
Dizziness	50mg	Pooled	2/47 [4.3]	2/45 [4.4]	1.0 (0.0 to 21.2)	28.47	-0.03 (-0.24 to 0.19)	27.24
Dizziness	Overall	Pooled	10/179 [5.6]	6/488 [1.2]	1.8 (0.3 to 10.2)	100	0.03 (-0.04 to 0.09)	100
Fatigue	100mg	Pandina, 2010[19] Risk of bias Low	3/35 [8.6]	2/33 [6.1]	1.4 (0.3 to 7.9)	12.97	0.03 (-0.10 to 0.15)	14.49
Fatigue	100mg	Winner, 2006[17] Low	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	5.46	-0.01 (-0.22 to 0.21)	4.86
Fatigue	100mg	Lewis, 2009[7] Low	2/35 [5.7]	2/33 [6.1]	0.9 (0.1 to 6.3)	10.67	0.00 (-0.12 to 0.11)	17.6
Fatigue	100mg	Pooled	6/83 [7.2]	5/78 [6.4]	1.1 (0.4 to 3.6)	29.1	0.01 (-0.07 to 0.09)	36.94
Fatigue	200mg	Winner, 2006[17] Low	2/14 [14.3]	1/12 [8.3]	1.7 (0.2 to 16.6)	7.47	0.06 (-0.18 to 0.30)	3.8

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Fatigue	200mg	Lewis, 2009[7] Low	3/35 [8.6]	2/33 [6.1]	1.4 (0.3 to 7.9)	12.97	0.03 (-0.10 to 0.15)	14.49
Fatigue	200mg	Winner, 2005[8] Moderate	7/112 [6.3]	6/50 [12.0]	0.5 (0.2 to 1.5)	35.79	-0.06 (-0.16 to 0.04)	21.8
Fatigue	200mg	Pooled	12/161 [7.5]	9/95 [9.5]	0.8 (0.3 to 1.8)	56.23	-0.02 (-0.09 to 0.06)	40.09
Fatigue	50mg	Pandina, 2010[19] Low	2/35 [5.7]	2/33 [6.1]	0.9 (0.1 to 6.3)	10.67	0.00 (-0.12 to 0.11)	17.6
Fatigue	50mg	Winner, 2006[17] Low	0/12 [0.0]	1/12 [8.3]	0.3 (0.0 to 7.5)	4	-0.08 (-0.29 to 0.12)	5.37
Fatigue	50mg	Pooled	2/47 [4.3]	3/45 [6.7]	0.7 (0.1 to 3.6)	14.67	-0.02 (-0.12 to 0.08)	22.97
Fatigue	Overall	Pooled	20/291 [6.9]	17/218 [7.8]	0.8 (0.5 to 1.6)	100	-0.01 (-0.06 to 0.04)	100
Injury	100mg	Winner, 2006[17] Low	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	6.65	-0.01 (-0.22 to 0.21)	7.74
Injury	100mg	Lewis, 2009[7] Low	3/35 [8.6]	2/33 [6.1]	1.4 (0.3 to 7.9)	15.79	0.03 (-0.10 to 0.15)	23.1
Injury	100mg	Pooled	4/48 [8.3]	3/45 [6.7]	1.2 (0.3 to 5.3)	22.44	0.02 (-0.09 to 0.12)	30.85
Injury	200mg	Winner, 2006[17] Low	1/14 [7.1]	1/12 [8.3]	0.9 (0.1 to 12.3)	6.63	-0.01 (-0.22 to 0.20)	8.25
Injury	200mg	Lewis, 2009[7] Low	4/35 [11.4]	2/33 [6.1]	1.9 (0.4 to 9.6)	17.7	0.05 (-0.08 to 0.19)	19.84
Injury	200mg	Winner, 2005[8] Moderate	8/112 [7.1]	6/50 [12.0]	0.6 (0.2 to 1.6)	46.56	-0.05 (-0.15 to 0.05)	33.87
Injury	200mg	Pooled	13/161 [8.1]	9/95 [9.5]	0.8 (0.4 to 1.9)	70.88	-0.01 (-0.09 to 0.06)	61.96
Injury	50mg	Winner, 2006[17] Low	1/12 [8.3]	1/12 [8.3]	1.0 (0.1 to 14.2)	6.67	0.00 (-0.22 to 0.22)	7.19
Injury	Overall	Pooled	18/221 [8.1]	13/152 [8.6]	0.9 (0.5 to 1.8)	100	0.00 (-0.06 to 0.06)	100
Insomnia	100mg	Pandina, 2010[19] Low	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	19.82	0.00 (-0.08 to 0.08)	32.51
Insomnia	100mg	Lewis, 2009[7] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	30.18	0.06 (-0.05 to 0.17)	17.49
Insomnia	100mg	Pooled	4/70 [5.7]	2/66 [3.0]	1.8 (0.3 to 10.2)	50	0.02 (-0.05 to 0.08)	50

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Insomnia	200mg	Lewis, 2009[7] Low	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	19.82	0.00 (-0.08 to 0.08)	32.51
Insomnia	50mg	Pandina, 2010[19] Low	3/35 [8.6]	1/33 [3.0]	2.8 (0.3 to 25.9)	30.18	0.06 (-0.05 to 0.17)	17.49
Insomnia	Overall	Pooled	8/140 [5.7]	4/132 [3.0]	1.8 (0.5 to 6.2)	100	0.02 (-0.03 to 0.06)	100
Mood problems	100mg	Pandina, 2010[19] Low	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	15.97	0.03 (-0.05 to 0.11)	39.29
Mood problems	100mg	Winner, 2006[17] Low	0/13 [0.0]	2/12 [16.7]	0.2 (0.0 to 3.5)	18.51	-0.17 (-0.40 to 0.07)	7.47
Mood problems	100mg	Pooled	1/48 [2.1]	2/45 [4.4]	0.7 (0.0 to 9.8)	34.48	-0.04 (-0.22 to 0.14)	46.75
Mood problems	200mg	Winner, 2006[17] Low	1/14 [7.1]	2/12 [16.7]	0.4 (0.0 to 4.2)	30.98	-0.10 (-0.35 to 0.16)	6.67
Mood problems	50mg	Pandina, 2010[19] Low	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	15.97	0.03 (-0.05 to 0.11)	39.29
Mood problems	50mg	Winner, 2006[17] Low	0/12 [0.0]	2/12 [16.7]	0.2 (0.0 to 3.8)	18.56	-0.17 (-0.41 to 0.07)	7.29
Mood problems	50mg	Pooled	2/61 [3.3]	4/57 [7.0]	0.7 (0.1 to 9.4)	34.53	-0.04 (-0.21 to 0.14)	46.58
Mood problems	Overall	Pooled	3/109 [2.8]	6/102 [5.9]	0.6 (0.2 to 2.1)	100	-0.01 (-0.08 to 0.06)	100
Nausea	100mg	Lewis, 2009[7] Low	2/35 [5.7]	2/33 [6.1]	0.9 (0.1 to 6.3)	23.74	0.00 (-0.12 to 0.11)	25.71
Nausea	200mg	Lewis, 2009[7] Low	3/35 [8.6]	2/33 [6.1]	1.4 (0.3 to 7.9)	28.84	0.03 (-0.10 to 0.15)	21.18
Nausea	200mg	Winner, 2005[8] Moderate	6/112 [5.4]	3/50 [6.0]	0.9 (0.2 to 3.4)	47.42	-0.01 (-0.08 to 0.07)	53.11
Nausea	200mg	Pooled	9/147 [6.1]	5/83 [6.0]	1.1 (0.4 to 3.1)	76.26	0.00 (-0.06 to 0.07)	74.29
Nausea	Overall	Pooled	11/182 [6.0]	7/116 [6.0]	1.0 (0.4 to 2.6)	100	0.00 (-0.06 to 0.06)	100
Nervousness	100mg	Pandina, 2010[19] Low	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	23.65	0.03 (-0.05 to 0.11)	29.56
Nervousness	100mg	Lewis, 2009[7] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	26.35	0.06 (-0.04 to 0.15)	20.44
Nervousness	100mg	Pooled	3/70 [4.3]	0/66 [0.0]	3.7 (0.4 to 32.7)	50	0.04 (-0.02 to 0.10)	50

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Nervousness	200mg	Lewis, 2009[7] Low	1/35 [2.9]	0/33 [0.0]	2.8 (0.1 to 67.2)	23.65	0.03 (-0.05 to 0.11)	29.56
Nervousness	50mg	Pandina, 2010[19] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	26.35	0.06 (-0.04 to 0.15)	20.44
Nervousness	Overall	Pooled	6/140 [4.3]	0/132 [0.0]	3.7 (0.8 to 17.3)	100	0.04 (0.00 to 0.08)	100
Paresthesia	100mg	Winner, 2006[17] Low	5/13 [38.5]	2/12 [16.7]	2.3 (0.5 to 9.7)	27.67	0.22 (-0.12 to 0.56)	1.97
Paresthesia	100mg	Lewis, 2009[7] Low	8/35 [22.9]	1/33 [3.0]	7.5 (1.0 to 57.1)	14.01	0.20 (0.05 to 0.35)	9.89
Paresthesia	**100mg**	**Pooled**	**13/48 [27.1]**	**3/45 [6.7]**	**3.4 (1.1 to 11.1)**	**41.68**	**0.20 (0.06 to 0.34)**	**11.86**
Paresthesia	200mg	Winner, 2006[17] Low	5/14 [35.7]	2/12 [16.7]	2.1 (0.5 to 9.1)	27.39	0.19 (-0.14 to 0.52)	2.1
Paresthesia	200mg	Lewis, 2009[7] Low	4/35 [11.4]	1/33 [3.0]	3.8 (0.4 to 32.0)	12.54	0.08 (-0.04 to 0.21)	15.5
Paresthesia	200mg	Winner, 2005[8] Moderate	9/112 [8.0]	0/50 [0.0]	8.6 (0.5 to 144.5)	7.19	0.08 (0.02 to 0.14)	67.27
Paresthesia	**200mg**	**Pooled**	**18/161 [11.2]**	**3/95 [3.2]**	**3.1 (1.0 to 9.3)**	**47.12**	**0.08 (0.03 to 0.14)**	**84.87**
Paresthesia	50mg	Winner, 2006[17] Low	1/12 [8.3]	2/12 [16.7]	0.5 (0.1 to 4.8)	11.2	-0.08 (-0.35 to 0.18)	3.27
Paresthesia	**Overall**	**Pooled**	**32/221 [14.5]**	**8/152 [5.3]**	**2.6 (1.2 to 5.6)**	**100**	**0.09 (0.05 to 0.14)**	**100**
Pharyngitis	100mg	Lewis, 2009[7] Low	1/35 [2.9]	3/33 [9.1]	0.3 (0.0 to 2.9)	8.81	-0.06 (-0.18 to 0.05)	39.86
Pharyngitis	200mg	Lewis, 2009[7] Low	3/35 [8.6]	3/33 [9.1]	0.9 (0.2 to 4.3)	18.47	-0.01 (-0.14 to 0.13)	27.71
Pharyngitis	200mg	Winner, 2005[8] Moderate	12/112 [10.7]	10/50 [20.0]	0.5 (0.2 to 1.2)	72.72	-0.09 (-0.22 to 0.03)	32.42
Pharyngitis	200mg	Pooled	15/147 [10.2]	13/83 [15.7]	0.6 (0.3 to 1.2)	91.19	-0.05 (-0.14 to 0.04)	60.14
Pharyngitis	Overall	Pooled	16/182 [8.8]	16/116 [13.8]	0.6 (0.3 to 1.1)	100	-0.06 (-0.13 to 0.02)	100
Sinusitis	100mg	Winner, 2006[17] Low	1/13 [7.7]	0/12 [0.0]	2.8 (0.1 to 62.5)	5.82	0.08 (-0.12 to 0.27)	6.34
Sinusitis	100mg	Lewis, 2009[7] Low	2/35 [5.7]	1/33 [3.0]	1.9 (0.2 to 19.8)	10.17	0.03 (-0.07 to 0.12)	25.26

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Sinusitis	100mg	Pooled	3/48 [6.3]	1/45 [2.2]	2.2 (0.3 to 14.2)	15.99	0.04 (-0.05 to 0.12)	31.6
Sinusitis	200mg	Winner, 2006[17] Low	2/14 [14.3]	0/12 [0.0]	4.3 (0.2 to 82.3)	6.5	0.14 (-0.07 to 0.36)	5.07
Sinusitis	200mg	Lewis, 2009[7] Low	1/35 [2.9]	1/33 [3.0]	0.9 (0.1 to 14.5)	7.55	0.00 (-0.08 to 0.08)	36.45
Sinusitis	200mg	Winner, 2005[8] Moderate	11/112 [9.8]	6/50 [12.0]	0.8 (0.3 to 2.1)	64.12	-0.02 (-0.13 to 0.08)	21.14
Sinusitis	200mg	Pooled	14/161 [8.7]	7/95 [7.4]	1.0 (0.4 to 2.2)	78.17	0.00 (-0.06 to 0.07)	62.67
Sinusitis	50mg	Winner, 2006[17] Low	1/12 [8.3]	0/12 [0.0]	3.0 (0.1 to 67.1)	5.83	0.08 (-0.12 to 0.29)	5.74
Sinusitis	Overall	Pooled	18/221 [8.1]	8/152 [5.3]	1.2 (0.5 to 2.5)	100	0.02 (-0.03 to 0.07)	100
Somnolence	100mg	Pandina, 2010[19] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	8.38	0.06 (-0.04 to 0.15)	26.65
Somnolence	100mg	Winner, 2006[17] Low	1/13 [7.7]	1/12 [8.3]	0.9 (0.1 to 13.2)	10.67	-0.01 (-0.22 to 0.21)	5.01
Somnolence	100mg	Pooled	3/48 [6.3]	1/45 [2.2]	1.9 (0.3 to 13.8)	19.05	0.05 (-0.04 to 0.13)	31.66
Somnolence	200mg	Winner, 2006[17] Low	2/14 [14.3]	1/12 [8.3]	1.7 (0.2 to 16.6)	14.6	0.06 (-0.18 to 0.30)	3.92
Somnolence	200mg	Lewis, 2009[7] Low	2/35 [5.7]	0/33 [0.0]	4.7 (0.2 to 94.8)	8.38	0.06 (-0.04 to 0.15)	26.65
Somnolence	200mg	Winner, 2005[8] Moderate	9/112 [8.0]	3/50 [6.0]	1.3 (0.4 to 4.7)	47.26	0.02 (-0.06 to 0.10)	33.12
Somnolence	200mg	Pooled	13/161 [8.1]	4/95 [4.2]	1.6 (0.6 to 4.6)	70.23	0.04 (-0.02 to 0.10)	63.69
Somnolence	50mg	Winner, 2006[17] Low	1/12 [8.3]	1/12 [8.3]	1.0 (0.1 to 14.2)	10.71	0.00 (-0.22 to 0.22)	4.65
Somnolence	Overall	Pooled	17/221 [7.7]	6/152 [3.9]	1.6 (0.7 to 3.8)	100	0.04 (-0.01 to 0.09)	100
Upper respiratory tract infection	100mg	Winner, 2006[17] Low	3/13 [23.1]	1/12 [8.3]	2.8 (0.3 to 23.1)	5.83	0.15 (-0.13 to 0.43)	7.57
Upper respiratory tract infection	100mg	Lewis, 2009[7] Low	7/35 [20.0]	3/33 [9.1]	2.2 (0.6 to 7.8)	16.37	0.11 (-0.06 to 0.27)	21.42
Upper respiratory tract infection	100mg	Pooled	10/48 [20.8]	4/45 [8.9]	2.3 (0.8 to 6.9)	22.2	0.12 (-0.02 to 0.26)	28.99

Appendix Table D52. Adverse effects with topiramate versus placebo in children (results from randomized controlled clinical trials) (continued)

Outcome	Dose	Reference, Risk of bias	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Upper respiratory tract infection	200mg	Winner, 2006[17] Low	3/14 [21.4]	1/12 [8.3]	2.6 (0.3 to 21.6)	5.8	0.13 (-0.14 to 0.40)	8.24
Upper respiratory tract infection	200mg	Lewis, 2009[7] Low	8/35 [22.9]	3/33 [9.1]	2.5 (0.7 to 8.7)	17.11	0.14 (-0.03 to 0.31)	20.09
Upper respiratory tract infection	200mg	Winner, 2005[8] Moderate	22/112 [19.6]	8/50 [16.0]	1.2 (0.6 to 2.6)	48.28	0.04 (-0.09 to 0.16)	36.99
Upper respiratory tract infection	200mg	Pooled	33/161 [20.5]	12/95 [12.6]	1.5 (0.8 to 2.8)	71.19	0.08 (-0.02 to 0.17)	65.32
Upper respiratory tract infection	50mg	Winner, 2006[17] Low	5/12 [41.7]	1/12 [8.3]	5.0 (0.7 to 36.7)	6.61	0.33 (0.01 to 0.65)	5.69
Upper respiratory tract infection	**Overall**	**Pooled**	**48/221 [21.7]**	**17/152 [11.2]**	**1.8 (1.1 to 3.1)**	**100**	**0.11 (0.03 to 0.18)**	**100**
Weight decrease	100mg	Winner, 2006[17] Low	2/13 [15.4]	1/12 [8.3]	1.8 (0.2 to 17.8)	4.49	0.07 (-0.18 to 0.32)	6.23
Weight decrease	100mg	Lewis, 2009[7] Low	10/35 [28.6]	7/33 [21.2]	1.3 (0.6 to 3.1)	32.69	0.07 (-0.13 to 0.28)	9.37
Weight decrease	100mg	Pooled	12/48 [25.0]	8/45 [17.8]	1.4 (0.6 to 3.1)	37.18	0.07 (-0.09 to 0.23)	15.6
Weight decrease	200mg	Winner, 2006[17] Low	4/14 [28.6]	1/12 [8.3]	3.4 (0.4 to 26.7)	5.49	0.20 (-0.08 to 0.49)	4.87
Weight decrease	200mg	Lewis, 2009[7] Low	17/35 [48.6]	7/33 [21.2]	2.3 (1.1 to 4.8)	42.12	0.27 (0.06 to 0.49)	8.36
Weight decrease	200mg	Winner, 2005[8] Moderate	11/112 [9.8]	2/50 [4.0]	2.5 (0.6 to 10.7)	10.7	0.06 (-0.02 to 0.14)	65.47
Weight decrease	**200mg**	**Pooled**	**32/161 [19.9]**	**10/95 [10.5]**	**2.4 (1.3 to 4.5)**	**58.31**	**0.14 (0.00 to 0.29)**	**78.71**
Weight decrease	50mg	Winner, 2006[17] Low	2/12 [16.7]	1/12 [8.3]	2.0 (0.2 to 19.2)	4.51	0.08 (-0.18 to 0.35)	5.69
Weight decrease	**Overall**	**Pooled**	**46/221 [20.8]**	**19/152 [12.5]**	**2.0 (1.2 to 3.2)**	**100**	**0.09 (0.02 to 0.15)**	**100**

Bold - significant at 95% confidence level

Appendix Table D53. Strength of evidence that drugs resulted in treatment discontinuation due to lack of efficacy (results from randomized controlled clinical trials)

Drug	Dose	Rate	RCTs	Children	Directness	Risk of bias	Consistency	Precision	Dose response	Strength of evidence	Conclusion
Divalproex sodium	1000mg	0.0 [1.4]	1	148	Yes	Low	Not applicable	No	Not applicable	Insufficient	Divalproex sodium 1000mg did not result in greater rates of treatment discontinuation due to lack of efficacy vs. placebo, the data is sparse
	250mg	1.2 [1.4]	1	156	Yes	Low	Not applicable	No	Not applicable	Insufficient	Divalproex sodium 250mg did not result in greater rates of treatment discontinuation due to lack of efficacy vs. placebo, the data is sparse
	500mg	4.1 [1.4]	1	147	Yes	Low	Not applicable	No	Not applicable	Insufficient	Divalproex sodium 500mg did not result in greater rates of treatment discontinuation due to lack of efficacy vs. placebo, the data is sparse

Appendix Table D54. Adverse effects with divalproex sodium versus placebo in children (pooled with random effects results from randomized controlled clinical trials)

Outcome	Dose	Reference, Risk of bias	Events/ randomized [rate] with drug	Events/ randomized [rate] with placebo	Relative risk (95% CI)	Weight	Absolute risk difference (95% CI)	Weight
Any adverse event	1000mg	Sheridan, 2008[6] Low	48/75 [64.0]	42/73 [58.0]	1.1 (0.9 to 1.4)	15.67	0.07 (-0.09 to 0.22)	16.11
	1000mg	Apostol, 2008[5] Low	48/75 [64.0]	42/73 [57.5]	1.1 (0.9 to 1.4)	15.67	0.07 (-0.09 to 0.22)	16.11
	1000mg	Pooled	96/150 [64.0]	84/146 [57.8]	1.1 (0.9 to 1.3)	31.35	0.07 (-0.05 to 0.18)	32.21
	250mg	Sheridan, 2008[6] Low	54/83 [65.0]	42/73 [58.0]	1.1 (0.9 to 1.5)	16.65	0.08 (-0.08 to 0.23)	16.99
	250mg	Apostol, 2008[5] Low	53/83 [63.9]	42/73 [57.5]	1.1 (0.9 to 1.4)	16.3	0.06 (-0.09 to 0.22)	16.87
	250mg	Pooled	107/166 [64.4]	84/146 [57.8]	1.1 (0.9 to 1.3)	32.95	0.07 (-0.04 to 0.18)	33.86
	500mg	Sheridan, 2008[6] Low	53/74 [72.0]	42/73 [58.0]	1.2 (1.0 to 1.6)	17.85	0.14 (-0.01 to 0.29)	16.97
	500mg	Apostol, 2008[5] Low	53/74 [71.6]	42/73 [57.5]	1.2 (1.0 to 1.6)	17.85	0.14 (-0.01 to 0.29)	16.97
	500mg	**Pooled**	**106/148 [71.8]**	**84/146 [57.8]**	**1.2 (1.0 to 1.5)**	**35.7**	**0.14 (0.03 to 0.25)**	**33.93**
	Overall	**Pooled**	**309/464 [66.6]**	**253/438 [57.8]**	**1.2 (1.0 to 1.3)**	**100**	**0.09 (0.03 to 0.16)**	**100**
Treatment discontinuation due to adverse events	1000mg	Sheridan, 2008[6] Low	7/75 [9.3]	1/73 [1.4]	6.8 (0.9 to 54.0)	25.4	0.08 (0.01 to 0.15)	13.73
	1000mg	Apostol, 2008[5] Low	7/75 [9.3]	1/73 [1.4]	6.8 (0.9 to 54.0)	25.4	0.08 (0.01 to 0.15)	13.73
	1000mg	Pooled	14/150 [9.3]	2/146 [1.4]	6.8 (1.6 to 29.5)	50.81	0.08 (0.03 to 0.13)	27.46
	250mg	Sheridan, 2008[6] Low	2/83 [2.4]	1/73 [1.4]	1.8 (0.2 to 19.0)	19.23	0.01 (-0.03 to 0.05)	23.38
	250mg	Apostol, 2008[5] Low	2/83 [2.4]	1/73 [1.4]	1.8 (0.2 to 19.0)	19.23	0.01 (-0.03 to 0.05)	23.38
	250mg	Pooled	4/166 [2.4]	2/146 [1.4]	1.8 (0.3 to 9.5)	38.45	0.01 (-0.02 to 0.04)	46.76
	500mg	Apostol, 2008[5] Low	0/74 [0.0]	1/73 [1.4]	0.3 (0.0 to 7.9)	10.74	-0.01 (-0.05 to 0.02)	25.78
	Overall	**Pooled**	**18/390 [4.6]**	**5/365 [1.4]**	**2.9 (1.0 to 8.3)**	**100**	**0.02 (-0.01 to 0.06)**	**100**

Bold - significant at 95% confidence level

Appendix Table D55. Adverse effects with divalproex sodium versus placebo in children (results from randomized controlled clinical trials)

Reference Risk of bias	Outcome	Dose	Events/ randomized [rate] with drug	Events/ randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Apostol, 2008[5] Low	Abdominal pain	1000mg	3/75 [4.0]	1/73 [1.4]	2.9 (0.3 to 27.4)	0.03 (-0.03 to 0.08)
	Abdominal pain	250mg	1/83 [1.2]	1/73 [1.4]	0.9 (0.1 to 13.8)	0.00 (-0.04 to 0.03)
	Abdominal pain	500mg	6/74 [8.1]	1/73 [1.4]	5.9 (0.7 to 48.0)	0.07 (0.00 to 0.14)
	Ammonia increased	1000mg	4/75 [5.3]	0/73 [0.0]	8.8 (0.5 to 159.9)	0.05 (0.00 to 0.11)
	Ammonia increased	1000mg	8/75 [10.7]	5/73 [6.8]	1.6 (0.5 to 4.5)	0.04 (-0.05 to 0.13)
	Ammonia increased	250mg	2/83 [2.4]	0/73 [0.0]	4.4 (0.2 to 90.3)	0.02 (-0.02 to 0.06)
	Ammonia increased	250mg	4/83 [4.8]	5/73 [6.8]	0.7 (0.2 to 2.5)	-0.02 (-0.09 to 0.05)
	Ammonia increased	500mg	1/74 [1.4]	0/73 [0.0]	3.0 (0.1 to 71.5)	0.01 (-0.02 to 0.05)
	Ammonia increased	500mg	2/74 [2.7]	5/73 [6.8]	0.4 (0.1 to 2.0)	-0.04 (-0.11 to 0.03)
	Cough	1000mg	2/75 [2.7]	3/73 [4.1]	0.6 (0.1 to 3.8)	-0.01 (-0.07 to 0.04)
	Cough	250mg	1/83 [1.2]	3/73 [4.1]	0.3 (0.0 to 2.8)	-0.03 (-0.08 to 0.02)
	Cough	500mg	4/74 [5.4]	3/73 [4.1]	1.3 (0.3 to 5.7)	0.01 (-0.06 to 0.08)
	Discontinued due to lack of efficacy	1000mg	0/75 [0.0]	1/73 [1.4]	0.3 (0.0 to 7.8)	-0.01 (-0.05 to 0.02)
	Discontinued due to lack of efficacy	250mg	1/83 [1.2]	1/73 [1.4]	0.9 (0.1 to 13.8)	0.00 (-0.04 to 0.03)
	Discontinued due to lack of efficacy	500mg	3/74 [4.1]	1/73 [1.4]	3.0 (0.3 to 27.8)	0.03 (-0.03 to 0.08)
	Fatigue	1000mg	6/75 [8.0]	4/73 [5.5]	1.5 (0.4 to 5.0)	0.03 (-0.06 to 0.11)
	Fatigue	250mg	1/83 [1.2]	4/73 [5.5]	0.2 (0.0 to 1.9)	-0.04 (-0.10 to 0.01)
	Fatigue	500mg	1/74 [1.4]	4/73 [5.5]	0.2 (0.0 to 2.2)	-0.04 (-0.10 to 0.02)
	Gastroenteritis viral	1000mg	4/75 [5.3]	1/73 [1.4]	3.9 (0.4 to 34.0)	0.04 (-0.02 to 0.10)
	Gastroenteritis viral	250mg	4/83 [4.8]	1/73 [1.4]	3.5 (0.4 to 30.8)	0.03 (-0.02 to 0.09)
	Gastroenteritis viral	500mg	1/74 [1.4]	1/73 [1.4]	1.0 (0.1 to 15.5)	0.00 (-0.04 to 0.04)
	Influenza	1000mg	3/75 [4.0]	5/73 [6.8]	0.6 (0.1 to 2.4)	-0.03 (-0.10 to 0.04)
	Influenza	250mg	1/83 [1.2]	5/73 [6.8]	0.2 (0.0 to 1.5)	-0.06 (-0.12 to 0.01)
	Influenza	500mg	5/74 [6.8]	5/73 [6.8]	1.0 (0.3 to 3.3)	0.00 (-0.08 to 0.08)
	Nasopharyngitis	1000mg	3/75 [4.0]	6/73 [8.2]	0.5 (0.1 to 1.9)	-0.04 (-0.12 to 0.03)
	Nasopharyngitis	250mg	5/83 [6.0]	6/73 [8.2]	0.7 (0.2 to 2.3)	-0.02 (-0.10 to 0.06)
	Nasopharyngitis	500mg	5/74 [6.8]	6/73 [8.2]	0.8 (0.3 to 2.6)	-0.01 (-0.10 to 0.07)
	Nausea	1000mg	7/75 [9.3]	3/73 [4.1]	2.3 (0.6 to 8.4)	0.05 (-0.03 to 0.13)
	Nausea	250mg	5/83 [6.0]	3/73 [4.1]	1.5 (0.4 to 5.9)	0.02 (-0.05 to 0.09)
	Nausea	500mg	6/74 [8.1]	3/73 [4.1]	2.0 (0.5 to 7.6)	0.04 (-0.04 to 0.12)
	Pharyngolaryngeal pain	1000mg	1/75 [1.3]	3/73 [4.1]	0.3 (0.0 to 3.0)	-0.03 (-0.08 to 0.02)
	Pharyngolaryngeal pain	250mg	1/83 [1.2]	3/73 [4.1]	0.3 (0.0 to 2.8)	-0.03 (-0.08 to 0.02)
	Pharyngolaryngeal pain	500mg	5/74 [6.8]	3/73 [4.1]	1.6 (0.4 to 6.6)	0.03 (-0.05 to 0.10)
	Somnolence	1000mg	4/75 [5.3]	1/73 [1.4]	3.9 (0.4 to 34.0)	0.04 (-0.02 to 0.10)
	Somnolence	250mg	2/83 [2.4]	1/73 [1.4]	1.8 (0.2 to 19.0)	0.01 (-0.03 to 0.05)
	Somnolence	500mg	4/74 [5.4]	1/73 [1.4]	3.9 (0.5 to 34.5)	0.04 (-0.02 to 0.10)

Appendix Table D55. Adverse effects with divalproex sodium versus placebo in children (results from randomized controlled clinical trials) (continued)

Reference Risk of bias	Outcome	Dose	Events/ randomized [rate] with drug	Events/ randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
	Treatment discontinuation	1000mg	13/75 [17.3]	6/73 [8.2]	2.1 (0.8 to 5.3)	0.09 (-0.02 to 0.20)
	Treatment discontinuation	250mg	8/83 [9.6]	6/73 [8.2]	1.2 (0.4 to 3.2)	0.01 (-0.08 to 0.10)
	Treatment discontinuation	500mg	12/74 [16.2]	6/73 [8.2]	2.0 (0.8 to 5.0)	0.08 (-0.03 to 0.18)
	Upper respiratory tract infection	1000mg	4/75 [5.3]	5/73 [6.8]	0.8 (0.2 to 2.8)	-0.02 (-0.09 to 0.06)
	Upper respiratory tract infection	250mg	12/83 [14.5]	5/73 [6.8]	2.1 (0.8 to 5.7)	0.08 (-0.02 to 0.17)
	Upper respiratory tract infection	500mg	3/74 [4.1]	5/73 [6.8]	0.6 (0.1 to 2.4)	-0.03 (-0.10 to 0.05)
	Viral infection	1000mg	0/75 [0.0]	2/73 [2.7]	0.2 (0.0 to 4.0)	-0.03 (-0.07 to 0.02)
	Viral infection	250mg	3/83 [3.6]	2/73 [2.7]	1.3 (0.2 to 7.7)	0.01 (-0.05 to 0.06)
	Viral infection	500mg	4/74 [5.4]	2/73 [2.7]	2.0 (0.4 to 10.4)	0.03 (-0.04 to 0.09)
	Vomiting	1000mg	3/75 [4.0]	1/73 [1.4]	2.9 (0.3 to 27.4)	0.03 (-0.03 to 0.08)
	Vomiting	250mg	2/83 [2.4]	1/73 [1.4]	1.8 (0.2 to 19.0)	0.01 (-0.03 to 0.05)
	Vomiting	500mg	4/74 [5.4]	1/73 [1.4]	3.9 (0.5 to 34.5)	0.04 (-0.02 to 0.10)
	Weight gain	1000mg	5/75 [6.7]	1/73 [1.4]	4.9 (0.6 to 40.7)	0.05 (-0.01 to 0.12)
	Weight gain	250mg	5/83 [6.0]	1/73 [1.4]	4.4 (0.5 to 36.8)	0.05 (-0.01 to 0.10)
	Weight gain	500mg	1/74 [1.4]	1/73 [1.4]	1.0 (0.1 to 15.5)	0.00 (-0.04 to 0.04)

Appendix Table D56. Treatment discontinuation with antidepressant trazodone versus placebo in children (results from low risk of bias randomized controlled clinical trial[4])

Outcome	Dose	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Treatment discontinuation	1mg/kg/day divided into 3 doses	2/20 [10.0]	3/20 [15.0]	0.7 (0.1 to 3.6)	-0.05 (-0.25 to 0.15)

Appendix Table D57. Adverse effects with propranolol, 80mg/day, versus placebo in children (results from moderate risk of bias randomized controlled clinical trial[32])

Outcome	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Abdominal pain	2/22 [9.1]	2/17 [11.8]	0.8 (0.1; 4.9)	-0.03 (-0.22; 0.17)
Amenorrhea	2/22 [9.1]	0/17 [0.0]	3.9 (0.2; 76.5)	0.09 (-0.06; 0.24)
Anorexia	1/22 [4.5]	0/17 [0.0]	2.3 (0.1; 54.3)	0.05 (-0.08; 0.17)
Depression	1/22 [4.5]	0/17 [0.0]	2.3 (0.1; 54.3)	0.05 (-0.08; 0.17)
Fatigue	3/22 [13.6]	0/17 [0.0]	5.5 (0.3; 99.4)	0.14 (-0.03; 0.30)
General worsening of behavior	2/22 [9.1]	0/17 [0.0]	3.9 (0.2; 76.5)	0.09 (-0.06; 0.24)
Increased appetite	3/22 [13.6]	1/17 [5.9]	2.3 (0.3; 20.4)	0.08 (-0.10; 0.26)
Menorrhagia	1/22 [4.5]	0/17 [0.0]	2.3 (0.1; 54.3)	0.05 (-0.08; 0.17)
Nausea	2/22 [9.1]	0/17 [0.0]	3.9 (0.2; 76.5)	0.09 (-0.06; 0.24)
Vomiting	1/22 [4.5]	0/17 [0.0]	2.3 (0.1; 54.3)	0.05 (-0.08; 0.17)
Weight gain	2/22 [9.1]	0/17 [0.0]	3.9 (0.2; 76.5)	0.09 (-0.06; 0.24)
Worsening of headache	2/22 [9.1]	1/17 [5.9]	1.5 (0.2; 15.7)	0.03 (-0.13; 0.20)

Appendix Table D58. Adverse effects with clonidine, 25-50µg/day, versus placebo in children (results from low risk of bias randomized controlled clinical trial[2])

Outcome	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Any adverse event	11/28 [39.3]	6/29 [20.7]	1.9 (0.8; 4.4)	0.19 (-0.05; 0.42)
Disturbed rhythms of the sleep-waking cycle and menstruation	1/28 [3.6]	0/29 [0.0]	3.1 (0.1; 73.1)	0.04 (-0.06; 0.13)
Fatigue	8/28 [28.6]	2/29 [6.9]	**4.1 (1.0; 17.8)**	**0.22 (0.03; 0.41)**
Irritability	0/28 [0.0]	1/29 [3.4]	0.3 (0.0; 8.1)	-0.03 (-0.13; 0.06)
Nausea	2/28 [7.1]	3/29 [10.3]	0.7 (0.1; 3.8)	-0.03 (-0.18; 0.11)
Pain in the right temporal region throughout treatment that ceased at the end of treatment	1/28 [3.6]	0/29 [0.0]	3.1 (0.1; 73.1)	0.04 (-0.06; 0.13)
Treatment discontinuation due to adverse events	1/28 [3.6]	0/29 [0.0]	3.1 (0.1; 73.1)	0.04 (-0.06; 0.13)

Bold - significant at 95% CI

Appendix Table D59. Adverse effects with magnesium, 9mg/kg/day, versus placebo in children (results from moderate risk of bias randomized controlled clinical trials)[21])

Outcome	Events/ Randomized [rate] with drug	Events/ Randomized [rate] with placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)
Diarrhea	11/58 [19.0]	4/60 [6.7]	2.8 (1.0 to 8.4)	0.12 (0.00 to 0.24)
Treatment discontinuation	16/58 [27.6]	16/60 [26.7]	1.0 (0.6 to 1.9)	0.01 (-0.15 to 0.17)
Treatment discontinuation because headache was resolved	1/58 [1.7]	2/60 [3.3]	0.5 (0.0 to 5.6)	-0.02 (-0.07 to 0.04)
Treatment discontinuation due to adverse events	3/58 [5.2]	1/60 [1.7]	3.1 (0.3 to 29.0)	0.04 (-0.03 to 0.10)

Appendix Table D60. Comparative safety of topiramate versus sodium valproate in preventing children migraine, results from individual randomized controlled clinical trials

Definition of the outcome	Active vs. control drug	Reference Risk of bias	Events/randomized in active control group Rate in active [control] group	Relative risk (95% CI)	Absolute risk difference (95% CI)
Nausea	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	Unalp, 2008[15] Unclear	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)
Mood changes	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	Unalp, 2008[15] Unclear	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)
Weight loss	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	Unalp, 2008[15] Unclear	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)
Weakness	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	Unalp, 2008[15] Unclear	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)
Raised liver transaminase	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	19073842 Unalp, 2008[15]	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)
Drowsiness	Topiramate, 1-3mg/kg vs. Sodium valproate,10-15mg/kg	Unalp, 2008[15] Unclear	1/28 0/20 3.6 [0.0]	2.2 (0.1 to 50.7)	0.04 (-0.07 to 0.14)

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Appendix E. Excluded Studies

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