

# Appendices

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# **Appendix A**

## Appendix A. Search Strategy

- 1 "restless leg\$ syndrome".mp.
- 2 "Ekbohm syndrome".mp.
- 3 Randomized Controlled Trials as Topic
- 4 randomized controlled trial/
- 5 random allocation/
- 6 double blind method/
- 7 single blind method/
- 8 clinical trial, phase [i.pt.](#)
- 9 clinical trial, phase [ii.pt.](#)
- 10 clinical trial, phase [iii.pt.](#)
- 11 clinical trial, phase [iv.pt.](#)
- 12 controlled clinical [trial.pt.](#)
- 13 randomized controlled [trial.pt.](#)
- 14 multicenter [study.pt.](#)
- 15 clinical [trial.pt.](#)
- 16 exp Clinical Trials as topic/
- 17 (clinical adj trial\$.tw.
- 18 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
- 19 PLACEBOS/
- 20 placebo\$.tw.
- 21 randomly [allocated.tw.](#)
- 22 (allocated adj2 random\$.tw.
- 23 or/3-22
- 24 or/1-2
- 25 24 and 23
- 26 (case reports or comment or editorial or historical article or letter or news or newspaper article or "review").pt.
- 27 25 not 26
- 28 Epidemiologic studies/
- 29 exp case control studies/
- 30 exp cohort studies/
- 31 case [control.tw.](#)
- 32 (cohort adj (study or studies)).tw.
- 33 (Follow up adj (study or studies)).tw.
- 34 (observational adj (study or studies)).tw.
- 35 [Longitudinal.tw.](#)
- 36 [Retrospective.tw.](#)
- 37 cross [sectional.tw.](#)
- 38 cross-sectional studies/
- 39 or/1-2

40 or/28-38

41 39 and 40

42 (case reports or comment or editorial or historical article or letter or news or newspaper article or "review").pt.

43 41 not 42

# **Appendix B**

## Appendix B. Excluded Trials

1. Bliwise DL, Freeman A, Ingram CD, et al. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Medicine*. 2005 Mar;6(2):141-7. PMID: 15716217. duration<4wks
2. Saletu M, Anderer P, Saletu-Zyhlarz GM, et al. Comparative placebo-controlled polysomnographic and psychometric studies on the acute effects of gabapentin versus ropinirole in restless legs syndrome. *Journal of Neural Transmission*. 2010 Apr;117(4):463-73. PMID: 20049491. duration<4wks
3. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *European Neuropsychopharmacology*. 2001 Apr;11(2):153-61. PMID: 11313161. duration<4wks
4. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *European Archives of Psychiatry & Clinical Neuroscience*. 2002 Aug;252(4):185-94. PMID: 12242580. duration<4wks
5. Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. *Neurology*. 1999 Jan 15;52(2):285-90. PMID: 9932945. *no primary outcome*
6. Davis BJ, Rajput A, Rajput ML, et al. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *European Neurology*. 2000;43(2):70-5. PMID: 10686463. *no primary outcome*
7. Earley CJ, Horska A, Mohamed MA, et al. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. *Sleep Medicine*. 2009 Feb;10(2):206-11. PMID: 18280205. *no primary outcome*
8. Happe S, Klosch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. *Neurology*. 2001 Nov 13;57(9):1717-9. PMID: 11706121. *no primary outcome*
9. Inoue Y, Hirata K, Kuroda K, et al. Efficacy and safety of pramipexole in Japanese patients with primary restless legs syndrome: A polysomnographic randomized, double-blind, placebo-controlled study. *Sleep Medicine*. 2010 Jan;11(1):11-6. PMID: 19962941. *no primary outcome*
10. Kutukcu Y, Dogruer E, Yetkin S, et al. Evaluation of periodic leg movements and associated transcranial magnetic stimulation parameters in restless legs syndrome. *Muscle & Nerve*. 2006 Jan;33(1):133-7. PMID: 16175624. *no primary outcome*
11. Zucconi M, Oldani A, Castronovo C, et al. Cabergoline is an effective single-drug treatment for restless legs syndrome: clinical and actigraphic evaluation. *Sleep*. 2003 Nov 1;26(7):815-8. PMID: 14655913. *no primary outcome*
12. Brodeur C, Montplaisir J, Godbout R, et al. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. *Neurology*. 1988 Dec;38(12):1845-8. PMID: 3057399. *no primary outcome*
13. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep*. 1993 Jun;16(4):327-32. PMID: 8341893. *no primary outcome*
14. Giannaki CD, Sakkas GK, Hadjigeorgiou GM, et al. Non-pharmacological management of periodic limb movements during hemodialysis session in patients with uremic restless legs syndrome. *ASAIO Journal*. 2010 Nov-Dec;56(6):538-42. PMID: 21245801. *no primary outcome*
15. Benes H, Kurella B, Kummer J, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep*. 1999 Dec 15;22(8):1073-81. PMID: 10617168. *no primary outcome*
16. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004 Aug 1;27(5):907-14. PMID: 15453549. *no primary outcome*
17. Trenkwalder C, Stiasny K, Pollmacher T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep*. 1995 Oct;18(8):681-8. PMID: 8560135. *no primary outcome*
18. Boghen D, Lamothe L, Elie R, et al. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. *Canadian Journal of Neurological Sciences*. 1986 Aug;13(3):245-7. PMID: 3527387. *no primary outcome*

19. Wagner ML, Walters AS, Coleman RG, et al. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep*. 1996 Jan;19(1):52-8. PMID: 8650464. *no primary outcome*
20. Sloand JA, Shelly MA, Feigin A, et al. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *American Journal of Kidney Diseases*. 2004 Apr;43(4):663-70. PMID: 15042543. *no primary outcome*
21. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *American Journal of Kidney Diseases*. 2001 Jul;38(1):104-8. PMID: 11431189. *no primary outcome*
22. von Scheele C. Levodopa in restless legs. *Lancet*. 1986 Aug 23;2(8504):426-7. PMID: 2874415. *non-randomized study design*
23. Adler CH. Treatment of restless legs syndrome with gabapentin. *Clinical Neuropharmacology*. 1997 Apr;20(2):148-51. PMID: 9099467. *non-randomized study design*
24. Akpınar S. Restless legs syndrome treatment with dopaminergic drugs. *Clinical Neuropharmacology*. 1987;10(1):69-79. PMID: 3545461. *non-randomized study design*
25. Hornyak M, Grossmann C, Kohnen R, et al. Cognitive behavioural group therapy to improve patients' strategies for coping with restless legs syndrome: a proof-of-concept trial. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008 Jul;79(7):823-5. PMID: 18303103. *non-randomized study design*
26. Micozkadioglu H, Ozdemir FN, Kut A, et al. Gabapentin versus levodopa for the treatment of Restless Legs Syndrome in hemodialysis patients: an open-label study. *Renal Failure*. 2004 Jul;26(4):393-7. PMID: 15462107. *non-randomized study design*
27. Pellecchia MT, Vitale C, Sabatini M, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clinical Neuropharmacology*. 2004 Jul-Aug;27(4):178-81. PMID: 15319704. *non-randomized study design*
28. Sakkas GK, Hadjigeorgiou GM, Karatzaferi C, et al. Intradialytic aerobic exercise training ameliorates symptoms of restless legs syndrome and improves functional capacity in patients on hemodialysis: a pilot study. *ASAIO Journal*. 2008 Mar-Apr;54(2):185-90. PMID: 18356653.
29. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *Journal of Clinical Psychiatry*. 1999 Apr;60(4):241-4. PMID: 10221285. *non-randomized study design*
30. Shinno H, Oka Y, Otsuki M, et al. Proposed dose equivalence between clonazepam and pramipexole in patients with restless legs syndrome. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010 Apr 16;34(3):522-6. PMID: 20156514. *non-randomized study design*
31. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology*. 1998 Dec;51(6):1599-602. PMID: 9855508. *not an intervention of interest*
32. Garcia-Borreguero D, Winkelmann J, Adams A, et al. Efficacy and tolerability of sumanirole in restless legs syndrome: a phase II, randomized, double-blind, placebo-controlled, dose-response study. *Sleep Medicine*. 2007 Mar;8(2):119-27. PMID: 17239657. *not an intervention of interest*
33. Hayes CA, Kingsley JR, Hamby KR, et al. The effect of endovenous laser ablation on restless legs syndrome. *Phlebology*. 2008;23(3):112-7. PMID: 18467618. *not an intervention of interest*
34. Hornyak M, Rupp A, Riemann D, et al. Low-dose hydrocortisone in the evening modulates symptom severity in restless legs syndrome. *Neurology*. 2008 Apr 29;70(18):1620-2. PMID: 18443313. *not an intervention of interest*
35. Jaber BL, Schiller B, Burkart JM, et al. Impact of short daily hemodialysis on restless legs symptoms and sleep disturbances. *Clinical Journal of The American Society of Nephrology: CJASN*. 2011 May;6(5):1049-56. PMID: 21415315. *not an intervention of interest*
36. Kushida CA, Walters AS, Becker P, et al. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. *Sleep*. 2009 Feb 1;32(2):159-68. PMID: 19238802. *not an intervention of interest*
37. Kushida CA, Becker PM, Ellenbogen AL, et al. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*. 2009 Feb 3;72(5):439-46. PMID: 19188575. *not an intervention of interest*
38. Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. *Chest*. 2009 Jan;135(1):74-80. PMID: 19017878. *not an intervention of interest*

39. Nahab FB, Peckham EL, Hallett M. Double-blind, placebo-controlled, pilot trial of botulinum toxin A in restless legs syndrome. *Neurology*. 2008 Sep 16;71(12):950-1. PMID: 18794499. *not an intervention of interest*
40. Pieta J, Millar T, Zacharias J, et al. Effect of pergolide on restless legs and leg movements in sleep in uremic patients. *Sleep*. 1998 Sep 15;21(6):617-22. PMID: 9779521. *not an intervention of interest*
41. Larsen S, Telstad W, Sorensen O, et al. Carbamazepine therapy in restless legs. Discrimination between responders and non-responders. *Acta Medica Scandinavica*. 1985;218(2):223-7. PMID: 3904337. *not an intervention of interest*
42. Sonka K, Pretl M, Kranda K. Management of restless legs syndrome by the partial D2-agonist terguride. *Sleep Medicine*. 2003 Sep;4(5):455-7. PMID: 14592288. *not an intervention of interest*
43. Staedt J, Wassmuth F, Ziemann U, et al. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. *Journal of Neural Transmission*. 1997;104(4-5):461-8. PMID: 9295178. *not an intervention of interest*
44. Telstad W, Sorensen O, Larsen S, et al. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *British Medical Journal Clinical Research Ed*. 1984 Feb 11;288(6415):444-6. PMID: 6419958. *not an intervention of interest*
45. Trenkwalder C, Hundemer HP, Lledo A, et al. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. *Neurology*. 2004 Apr 27;62(8):1391-7. PMID: 15111679. *not an intervention of interest*
46. Walters AS, Hening WA, Kavey N, et al. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Annals of Neurology*. 1988 Sep;24(3):455-8. PMID: 3067654. *not an intervention of interest*
47. Wetter TC, Stiasny K, Winkelmann J, et al. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology*. 1999 Mar 23;52(5):944-50. PMID: 10102410. *not an intervention of interest*
48. Giorgi L, Ritchie SY, Kirsch JM. Efficacy and tolerability of ropinirole in patients with restless legs syndrome and a baseline IRLS total score > or = 24 points--data from the ropinirole clinical trial programme. *Current Medical Research & Opinion*. 2006 Oct;22(10):1867-77. PMID: 17022844. *not a primary study*

# **Appendix C**

**Appendix C. Table 1. Evidence Table for primary RLS: dopamine agonist trials**

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Study ID</b> Högl, 2011<sup>1</sup></p> <p><b>Geographical Location:</b> Europe</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> parallel design, dose-titration</p> <p><b>Duration:</b> 26 weeks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>Adults 8 to 85 years of age, meeting diagnostic criteria of the IRLS (&gt;15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months.</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>serum ferritin ≤ 30 ng/mL</li> <li>known hypersensitivity to pramipexole</li> <li>augmentation during previous RLS treatment, unsuccessful previous treatment with non-ergotamine dopamine agonists (e.g. pramipexole, ropinirole)</li> <li>any non-RLS sleep disorder</li> <li>any major psychiatric disorder within last 2 years, change in any antidepressant regimen with last 4 weeks (or any anticipated change)</li> <li>any use of dopamine agonists, levodopa, or any medication or dietary supplement capable or altering RLS symptoms</li> <li>women with child bearing potential (pregnant, breastfeeding women, inadequate contraception)</li> </ul>	<p><b>N</b>=331 (2 patients not included in demographic data)</p> <p><b>Age</b> (mean yr): 56.9</p> <p><b>Gender (Male %):</b> 40.4</p> <p><b>Race/Ethnicity (%)</b>: NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> <i>See inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 23.7</p> <p><b>Previous RLS medication history:</b> NR (see exclusion criteria)</p> <p><b>Iron Status:</b> patients with serum ferritin ≤30 ng/m excluded</p>	<p><b>Intervention:</b> Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) (n=166)</p> <p><b>Comparator:</b> Placebo (n=163)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score</p> <p><b>B. Quality of life</b> RLS-QoL</p> <p><b>Subjective Sleep Quality</b> RLS-6</p> <p><b>Definition of clinically significant Improvement:</b> 4.5 point difference between pramipexole and placebo at week 26</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnel, Incomplete outcome data: yes, 2 patients did not receive any treatment Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b></p>
<p><b>Study ID</b> Montagna, 2011<sup>2</sup></p> <p><b>Geographical Location:</b> International (52 hospitals, specialist</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>age 18 to 80 years</li> <li>RLS diagnosed with IRLSSG criteria</li> <li>RLS Severity; IRLS&gt;15 (AND)</li> <li>IRLS item 10 scale score ≥ 2 (i.e., at least moderate RLS-</li> </ul>	<p><b>N</b>=362</p> <p><b>Age</b> (mean, yr): 55.5</p> <p><b>Gender (Male %):</b> 30</p> <p><b>Race/Ethnicity (%)</b>: White 86</p>	<p><b>Intervention:</b> Pramipexole (n=203), daily, 1-3 hrs before bedtime. Dose started at 0.25 mg/day and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes,</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p>offices, and primary care centers in Finland, France, Germany, Ireland, Italy, Korea, Spain, Sweden and the United Kingdom)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group</p> <p><b>Duration:</b> 12 wks</p>	<p>associated mood disturbance)</p> <ul style="list-style-type: none"> <li>• RLS symptoms present <math>\geq 2</math> days per week during the prior two months</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• patients with baseline Beck Depression Inventory-II score <math>&gt;28</math>, with current presence of major depression, psychosis, or any other severe mental disorder requiring medical therapy or history of suicidal ideation</li> <li>• any clinical condition that could interfere with study participation or evaluation of results or that could increase patient's health risk</li> <li>• concomitant or prior treatment (within 2 wks) with any drug that could influence RLS symptoms or depressive symptoms (e.g., anxiolytics or hypnotics) was forbidden</li> <li>• pregnant or breast feeding women</li> </ul>	<p>I: White (86.7), Black (0.0), Asian (13.3) C: : White (86.0), Black (0.5), Asian (13.5)</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Baseline Severity:</b> Severe RLS Baseline mean IRLS score: 25.9</p> <p><b>Previous RLS medication history:</b> Previous treatment I: 27.5% C: 29.1%</p> <p><b>Iron Status:</b> NR</p>	<p><b>Comparator:</b> Placebo (n=201)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p> <p><b>B. Quality of life</b> RLS QoL</p> <p><b>Subjective Sleep Quality</b> NR</p> <p><b>Definition of clinically significant Improvement:</b> Responders for IRLS scale score defined as those with <math>\geq 50\%</math> improvement from baseline</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p>
<p><b>Study ID</b> Oertel, 2010<sup>3</sup></p> <p><b>Geographical Location:</b> Europe (Austria, Finland, Germany, Italy and Spain)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Male and female subjects aged 18-75 yrs</li> <li>• RLS diagnosed with IRLSSG criteria</li> <li>• De novo subjects; i.e., no previous dopaminergic RLS treatment or previous positive response to dopaminergic RLS treatment</li> <li>• PLM index (PLMI) score of <math>\geq 15</math> PLM/h time in bed as documented using polysomnography, AND</li> </ul>	<p><b>N</b>=362</p> <p><b>Age</b> (mean yr): 59.4</p> <p><b>Gender (Male %):</b> 26</p> <p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLS criteria</p>	<p><b>Intervention:</b> Ritigotine transdermal patch, dose ranging from 1 mg/24 hour to optimal dose or a maximum dose of 3mg/ 24hr (n=46)</p> <p><b>Comparator:</b> Placebo (n=20)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score % of responders on CGI-I scale Score</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: Yes Allocation concealment: Yes Blinding of participants and personnel, outcome assessors Yes</p> <p>Incomplete outcome data: yes, had to have received at least one dose of study medication, a valid baseline assessment and at least 1 post-baseline assessment</p> <p>Selective outcome reporting: no</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<b>Duration:</b> 4 wks	<p>IRLSSG rating scale score <math>\geq 15</math> AND CGI item 1, severity of symptom score <math>\geq 4</math></p> <ul style="list-style-type: none"> <li>ability to remove/apply patches correctly and consistently</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>previous Rotigotine treatment</li> <li>secondary RLS</li> <li>history of sleep disturbances other than owing to RLS</li> <li>treatment with dopamine agonists within 28 days or levodopa within 7 days prior to baseline visit</li> <li>concomitant diseases such as attention deficit hyperactivity disorder, polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs or moving toes, or radiculopathy; other central nervous system disorders such as Parkinson's disease, dementia, progressive supranuclear palsy, multiple system atrophy, Huntington's chorea, Alzheimer's.</li> <li>previous psychotic episodes</li> <li>skin hypersensitivity to adhesives or other transdermals</li> <li>clinically relevant cardiac, renal, or hepatic dysfunction; venous or arterial peripheral vascular disease; or symptomatic orthostatic hypertension</li> <li>concomitant treatment with neuroleptics, hypnotics,</li> </ul>	<p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 26</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status:</b> NR</p>	<p><b>B. Quality of life</b> NR</p> <p><b>Subjective Sleep Quality</b> MOS sleep scale</p> <p><b>Length of follow-up</b></p> <p><b>Definition of clinically significant Improvement:</b> Responders defined as:</p> <ul style="list-style-type: none"> <li><math>\geq 50\%</math> score improvement in IRLS scale at the end of maintenance phase vs. baseline</li> </ul> <p>Remitters</p> <ul style="list-style-type: none"> <li>IRLSSG rating scale <math>\leq 10</math> or IRLS score =0 at the end of maintenance</li> </ul> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b></p> <p><b>Notes</b> "sponsor was involved in the design of the study, analysis and interpretation of the data, writing of the report, and in the decision to submit the paper for publication"</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	<p>antidepressants, anxiolytics, anticonvulsants, budipine, opioids, benzodiazepenes, monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors, sedative antihistamines, psychostimulants, amphetamines, or dopamine antagonist antiemetics except domperidone.</p> <ul style="list-style-type: none"> <li>• pregnant or nursing women; women without effective contraceptive methods</li> <li>• subjects with work-related irregular sleep patterns</li> </ul>			
<p><b>Study ID</b> Ferini-Strambi, 2008<sup>4</sup></p> <p>Geographical Location: Europe</p> <p>Funding source: Industry</p> <p>Study Design: parallel design, flexible dose</p> <p>Duration: 12 weeks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• adults, 18 to 80 years of age, meeting diagnostic criteria of the IRLS (&gt;15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months.</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• clinically significant liver or renal disease, insulin-dependent diabetes, clinically significant laboratory abnormalities</li> <li>• present or past history of another sleep disorder</li> <li>• major depression, psychiatric disorders, suicidal behavior/ ideation</li> <li>• malignant melanoma</li> <li>• women who were pregnant, lactating, or of child bearing potential and did not use or had inadequate contraception</li> </ul>	<p><b>N</b>=369</p> <p><b>Age</b> (mean yr): 56.6</p> <p><b>Gender</b> (Male %): 32</p> <p><b>Race/Ethnicity</b> (%): white 99.5</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> <i>See inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe symptoms. Baseline mean IRLS score: 24.4</p> <p><b>Previous RLS medication history:</b> 26.6%</p> <p><b>Iron Status:</b> NR</p>	<p><b>Intervention:</b> Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) and tolerability (n=182)</p> <p><b>Comparator:</b> Placebo (n=187)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score PGI Scale Score</p> <p><b>B. Quality of life</b> RLS-QoL</p> <p><b>Subjective Sleep Quality</b> Medical Outcomes Study (MOS) Sleep Scale</p> <p><b>Definition of clinically significant Improvement:</b> none</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: adequate Allocation concealment: adequate (blister packs) Blinding: patients, investigators, and study personnel, Incomplete outcome data: Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b></p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<b>Study ID</b> Kushida, 2008 <sup>5</sup>  <b>Geographical Location:</b> USA Multi center trial  <b>Funding source:</b> Industry  <b>Study Design:</b> Parallel group  <b>Duration:</b> 12 wks	<ul style="list-style-type: none"> <li>current use of medications that might affect RLS symptoms (e.g. levodopa, dopamine agonists, or antidepressants)</li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>age 18 to 79 years</li> <li>RLS diagnosed with IRLS criteria, IRLS &gt;20 points</li> <li>baseline score ≥15 on the Insomnia severity index</li> <li>symptom onset no later than 5 pm</li> <li>≥15 nights of RLS symptoms during the previous month</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>secondary RLS</li> <li>patients who had experienced augmentation or rebound with previous treatment</li> <li>patients with other primary sleep disorders, movement disorders or medical conditions that would affect the assessment of RLS</li> <li>experiencing daytime RLS symptoms that required treatment</li> <li>taking medications known to affect RLS or sleep</li> <li>experiencing withdrawal/ introduction/dose change of medications known to inhibit or induce P450CYP1A2</li> </ul>	<p>N=362</p> <p><b>Age</b> (mean yr): 50.9</p> <p><b>Gender</b> (Male %): 40</p> <p><b>Race/Ethnicity (%)</b>: NR</p> <p><b>Comorbidities</b>: NR</p> <p><b>Criteria used to define RLS</b> IRLS criteria</p> <p><b>Baseline Severity</b>: Moderate-Severe. Baseline mean IRLS score: 26</p> <p><b>Previous RLS medication history</b>: NR</p> <p><b>Iron Status</b>: NR</p>	<p><b>Intervention</b>: Ropinirole 0.5-6.0 mg/d twice daily in 2 equally divided doses (n=175)</p> <p><b>Comparator</b>: Placebo (n=184)</p> <p><b>Outcomes reported:</b>  <b>A. Change in Disease Status and Impact</b>  IRLS Scale Score  % of responders on CGI-I scale Score</p> <p><b>B. Quality of life</b> NR</p> <p><b>Subjective Sleep Quality</b></p> <p><b>Length of follow-up</b></p> <p><b>Definition of clinically significant Improvement:</b>  Responders defined as those who rated very much improved or much improved on CGI-I or PGI scale scores</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b>  Sequence generation: NR  Allocation concealment: NR  Blinding of participants and personnel, outcome assessors NR  Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b>  (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b></p> <ul style="list-style-type: none"> <li>No description of randomization procedures</li> <li>No description of participant baseline characteristics except for age, gender and disease severity</li> </ul> <p><b>Notes</b></p>
<b>Study ID</b> Trenkwalder, 2008 <sup>6</sup>  <b>Geographical Location:</b>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>age 18 to 79 years</li> <li>idiopathic RLS diagnosed with IRLS criteria, IRLS &gt;20 points</li> <li>either no previous</li> </ul>	<p>N=458</p> <p><b>Age</b> (mean, yr): 57.7</p> <p><b>Gender (Male %):</b> 27</p>	<p><b>Intervention:</b>  Rotigotine 1mg/24hr (n=115)  Rotigotine 2mg/24 hr (n=112)  Rotigotine 3mg/24 hr (n=114)</p>	<p><b>Assessment of Internal Validity</b>  Sequence generation: yes  Allocation concealment: yes  Blinding of participants and personnel, outcome assessors</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p>Europe (49 centers in Austria, Finland, Germany, Italy, Netherlands, Spain, Sweden, UK)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group, fixed-dose</p> <p><b>Duration:</b> 6 months</p>	<p>dopaminergic medication for RLS or positive response to dopaminergic treatment</p> <ul style="list-style-type: none"> <li>• ≥15 points on IRLS scale, a score of ≥4 on CGI item 1 for disease severity</li> <li>• ability to remove apply patches correctly and consistently</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• secondary RLS</li> <li>• current history of sleep disturbances (sleep apnea syndrome, narcolepsy,</li> <li>• concomitant treatment with several types of drug (neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsives, opioids, benzodiazepines, monoamine oxidase inhibitors, catechol-O methyltransferase inhibitors, sedative anti histamines, psychostimulants, or amphetamines)</li> <li>• concomitant diseases such as polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and moving toes, orradiculopathy; other CNS diseases (eg, Parkinson's disease, dementia, progressive supranuclear palsy, multisystem atrophy, Huntington's disease, amyotrophic lateral sclerosis, or Alzheimer's disease);</li> <li>• previous psychotic episodes</li> </ul>	<p><b>Race/Ethnicity (%):</b> White 99</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 28.1</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status:</b> NR</p>	<p><b>Comparator:</b> Placebo (n=117)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I scale Score</p> <p><b>B. Quality of life</b> RLS QoL Generic health related quality of life SF-36)</p> <p><b>Subjective Sleep Quality</b> MOS sleep scale</p> <p><b>Definition of clinically significant Improvement:</b> Remission (IRLS sum score=0 or &lt;10 ) Responders defined as having minimum 50% improvement from baseline in IRLS score or a CGI item 2 rating of "much improved"</p> <p><b>Adverse Effects Reported:</b> yes Severity of Augmentation assessed with ASRS scale score</p>	<p>yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b> Not ITT; patients analyzed different from patients randomized Study sponsor involved in conception and design of the study and in data analysis and interpretation but had no role in data collection</p> <p><b>Notes</b></p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	<ul style="list-style-type: none"> <li>• skin hypersensitivity to adhesives or other transdermal preparations;</li> <li>• myocardial infarction over the past 12 months</li> <li>• clinically relevant cardiac, renal or hepatic dysfunction</li> <li>• arterial peripheral vascular disease</li> <li>• Qtc interval of 500 ms or longer at screening</li> <li>• symptomatic orthostatic hypotension at screening or baseline</li> <li>• intake of investigational drug 28 days before baseline visit</li> <li>• pregnant or lactating women</li> <li>• women without effective contraceptive methods</li> <li>• patients with work-related irregular sleep patterns</li> </ul>			
<p><b>Study ID</b> Oertel, 2007<sup>7</sup></p> <p><b>Geographical Location:</b> Europe</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> parallel design, dose-response</p> <p><b>Duration:</b> 6 weeks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• male and female patients, 18 to 80 years of age, with a diagnosis of primary RLS based on IRLS criteria (score &gt;15 points)</li> <li>• RLS symptoms present for at least 2 to 3 days per week in the 3 months before study entry.</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• pregnant, breastfeeding women or using inadequate contraception</li> <li>• diabetic or had significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders, other neurologic disease</li> <li>• sleep disorders unrelated to</li> </ul>	<p><b>N</b>=345</p> <p><b>Age</b> (mean yr): 55.5</p> <p><b>Gender</b> (Male %): 34</p> <p><b>Race/Ethnicity</b> (%): white 99</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> <i>See inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe symptoms. Baseline mean IRLS score: 24.8</p> <p><b>Previous RLS medication history:</b> 31%. All pharmacologic treatment for RLS was discontinued within</p>	<p><b>Intervention:</b> Pramipexole 0.125 mg and could be increased up to 0.75 mg according to the Patient Global Impression scale (PGI) rating and overall tolerability of the drug (n=230)</p> <p><b>Comparator:</b> Placebo (n=115)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score</p> <p><b>B. Quality of life</b> NR</p> <p><b>Subjective Sleep Quality</b> none</p> <p><b>Definition of clinically</b></p>	<p><b>Assessment of Internal Validity</b> Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnel Incomplete outcome data: yes, had to have received one dose of study drug Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b> [General comments on quality of</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	RLS, psychotic disorders <ul style="list-style-type: none"> <li>• mental disorders, patients with a history of substance abuse.</li> </ul>	14 days before the study's start  <b>Iron Status:</b> NR	<b>significant Improvement:</b> IRLS responders if they had an at least 50% reduction in their baseline IRLS score at week 6  <b>Adverse Effects Reported:</b> yes	reporting, adequateness of statistical analysis]
<b>Study ID</b> Adler, 2004 <sup>8</sup>  <b>Geographical Location:</b> US  <b>Funding source:</b> Industry  <b>Study Design:</b> crossover  <b>Duration:</b> 4 weeks of placebo then ropinirole or ropinirole then placebo with a 1-week wash-out between treatments	<b>Inclusion criteria:</b> <ul style="list-style-type: none"> <li>• IRLS criteria for RLS and needed a IRLS score <math>\geq 10</math>. Patients were not allowed to be on RLS medication for at least 2 weeks prior to the baseline visit.</li> </ul> <b>Exclusion criteria:</b> <ul style="list-style-type: none"> <li>• previous use of ropinirole, secondary RLS</li> <li>• significant medical disease that would not allow use of ropinirole</li> <li>• an inability to complete diary forms</li> <li>• pregnancy or lactation.</li> </ul>	<b>N=22</b>  <b>Age</b> (mean yr): 60  <b>Gender</b> (Male %): 27  <b>Race/Ethnicity (%)</b> : NR  <b>Comorbidities:</b> NR  <b>Criteria used to define RLS</b> baseline total score $\geq 10$ points on IRLS  <b>Baseline Severity:</b> moderate to severe symptoms. Baseline mean IRLS score: 25.9  <b>Previous RLS medication history:</b> NR, none with ropinirole	<b>Intervention:</b> Ropinirole 0.5 to 6.0 mg (n=22)  <b>Comparator:</b> Placebo (n=22)  <b>A. Change in Disease Status and Impact</b> IRLS Scale Score Global change score (-3 markedly worse to +3 markedly improved)  <b>B. Quality of life</b> none  <b>Subjective Sleep Quality</b> Epworth Sleepiness Scale  <b>Definition of clinically significant Improvement:</b> none	<b>Assessment of Internal Validity</b> Sequence generation: not defined Allocation concealment: adequate, packaging identical in appearance Blinding: patients, investigators Incomplete outcome data: no Selective outcome reporting: no  <b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)  <b>Reviewer Comments</b>
<b>Study ID</b> Bogan, 2006 <sup>9</sup>  <b>Geographical Location:</b> US  <b>Funding source:</b> Industry  <b>Study Design:</b> parallel design, flexible dose	<b>Inclusion criteria:</b> <ul style="list-style-type: none"> <li>• adults, aged 18 to 79 years, with a diagnosis of primary RLS, using the IRLS diagnostic criteria (baseline total score <math>\geq 15</math> points</li> <li>• <math>\geq 15</math> nights of RLS symptoms during the previous month, and documented RLS symptoms for at least 4 of the 7 nights during the screening/washout phase (between the screening visit and baseline visit)).</li> </ul>	<b>N=381</b>  <b>Age</b> (mean yr): 52.3  <b>Gender</b> (Male %): 39  <b>Race/Ethnicity (%)</b> : NR  <b>Comorbidities:</b> NR  <b>Criteria used to define RLS</b> <i>See inclusion criteria</i>  <b>Baseline Severity:</b> moderate to	<b>Adverse Effects Reported:</b> yes <b>Intervention:</b> Ropinirole 0.25-4.0 mg (n=187)  <b>Comparator:</b> Placebo (n=194)  <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score  <b>B. Quality of life</b> Johns Hopkins RLS Quality of Life questionnaire	<b>Assessment of Internal Validity</b> Sequence generation: not defined Allocation concealment: adequate, packaging identical in appearance Blinding: patients, investigators, site monitors Incomplete outcome data: 1 patient from the placebo group did not receive any study medication Selective outcome reporting: no  <b>Applicability</b> (Eligibility criterion for inclusion,

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Duration:</b> 12 weeks</p>	<p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• signs of secondary RLS, including renal failure, pregnancy, and iron deficiency anemia. Iron deficiency was determined by each investigator based on clinical judgment of serum iron, ferritin, iron binding capacity, and percent saturation data obtained in each patient at screening.</li> <li>• patients who had experienced augmentation or rebound with previous treatment or had daytime symptoms as a part of their usual RLS symptom pattern were also excluded.</li> </ul>	<p>severe symptoms. Baseline mean IRLS score: 22</p> <p><b>Previous RLS medication history:</b> NR but patients who had experienced augmentation or rebound with previous treatment were excluded</p> <p><b>Iron Status:</b> subjects with iron deficiency anemia excluded</p>	<p><b>Subjective Sleep Quality</b> Medical Outcomes Study (MOS) Sleep Scale</p> <p><b>Definition of clinically significant Improvement:</b> NR</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b> [General comments on quality of reporting, adequateness of statistical analysis]</p>
<p><b>Study ID</b> Montplasil, 2006<sup>10</sup></p> <p><b>Geographical Location:</b> 18 centers in Australia, Austria, Canada, Germany and South Africa</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group</p> <p><b>Duration:</b> 12 wks (Trial consisted of 24-wk single blind phase during which all patients received ropinirole followed by 12 wk</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• age 18 to 80 years</li> <li>• male or female patients</li> <li>• RLS diagnosed with IRLS criteria (IRLS <math>\geq</math>15 points)</li> <li>• <math>\geq</math>15 nights of RLS symptoms during the previous month; for patients who had been receiving treatment for RLS investigators used their best clinical judgment to assess whether or not the patient would have experienced a minimum of 15 nights of symptoms if the patient had not been treated</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• patients with other primary sleep disorders that might affect the symptoms of RLS</li> <li>• patients with movement disorders</li> </ul>	<p><b>N</b>=362</p> <p><b>Age</b> (mean (SD), yr): 53.5</p> <p><b>Gender (Male %):</b> 45</p> <p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: initially 26 (single-blind phase)</p> <p><b>Previous RLS medication history:</b> NR</p>	<p><b>Intervention</b> Ropinirole (n=45) daily, 1-3 hrs before bedtime. Doses started at 0.25mg/day and titrated upwards to a maximum dose of 4 mg/day.</p> <p><b>Comparator:</b> Placebo (n=47)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I scale Score</p> <p><b>B. Quality of life</b> RLS QoL Generic health related quality of life SF-36)</p> <p><b>Subjective Sleep Quality</b> MOS sleep scale</p> <p><b>Definition of clinically</b></p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p>

<b>Study Characteristics and Design</b>	<b>Inclusion/Exclusion criteria</b>	<b>Participant Characteristics</b>	<b>Intervention (daily dose) /Comparator (daily dose)</b>	<b>Risk of bias and Applicability</b>
double blind, placebo controlled phase for treatment responders defined as those with reduction in total IRLS score of at least 6 points from baseline)	<ul style="list-style-type: none"> <li>patients with a medical condition that would affect assessment of RLS or the tolerability of ropinirole</li> <li>experiencing daytime RLS symptoms that required treatment</li> <li>experiencing augmentation or end of dose rebound from previous therapy</li> <li>secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy)</li> <li>history of alcohol or drug abuse</li> <li>previous intolerance to dopamine agonists</li> </ul>	<b>Iron Status:</b> NR	<b>significant Improvement:</b> NR  <b>Adverse Effects Reported:</b> yes	<b>Reviewer Comments Notes</b>
<b>Study ID</b> Winkelman, 2006 <sup>11</sup>  <b>Geographical Location:</b> United States Multicenter Trial(43 Sites)  <b>Funding source:</b> Industry  <b>Study Design:</b> Parallel group ( 4 arms; comparison of 3 fixed doses of pramipexole with placebo)  <b>Duration:</b> 12 wks	<b>Inclusion criteria:</b> <ul style="list-style-type: none"> <li>adults (age 18 to 80 years)</li> <li>RLS diagnosed with IRLSSG criteria</li> <li>moderate to severe disease; IRLS score&gt;15 and symptoms at least 2 to 3 days per week for at least the previous 3 months</li> </ul> <b>Exclusion criteria:</b> <ul style="list-style-type: none"> <li>recent RLS treatment (concurrently or during the prior 2 wks)</li> <li>history of failed RLS treatment</li> <li>recent use of dietary supplement or medication with potential to affect RLS symptoms</li> <li>any medical condition that could affect assessment or contraindicate pramipexole</li> <li>any sleep disorder other than RLS</li> </ul>	<b>N=345</b>  <b>Age</b> (mean, yr): 51.4  <b>Gender (Male %):</b> 38%  <b>Race/Ethnicity (%):</b> %White=97.3  <b>Comorbidities:</b> NR  <b>Criteria used to define RLS</b> IRLSSG criteria  <b>Baseline Severity:</b> Moderate-Severe disease. Baseline mean IRLS score: 23.5  <b>Previous RLS medication history:</b> NR  <b>Iron Status:</b> NR	<b>Intervention:</b> Pramipexole (n=254) at fixed doses of 0.25 (n=89), 0.5 (n=80) and 0.75 (n=90) mg/day, taken each evening 2 to 3hrs before anticipated bedtime  <b>Comparator:</b> Placebo (n=86)  <b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I Scale Score  <b>B. Quality of life</b> RLS-QoL <b>Subjective Sleep Quality</b> Epworth Sleepiness Scale (ESS)  <b>Length of follow-up</b>  <b>Definition of clinically significant Improvement:</b> Responder= patient with CGI-I	<b>Assessment of Internal Validity</b> Sequence generation: yes, computer generated randomization schedule Allocation concealment: unclear Blinding of participants and personnel, outcome assessors Yes Incomplete outcome data: yes, had to have received one dose of study drug Selective outcome reporting: no  <b>Applicability</b>  <b>Reviewer Comments</b> [General comments on quality of reporting, adequateness of statistical analysis]

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Study ID</b> Trenkwalder, 2004<sup>12</sup></p> <p><b>Geographical Location:</b> Europe (43 hospitals and sleep clinics in: Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group</p> <p><b>Duration:</b> 12 wks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• age 18 to 79 years</li> <li>• RLS diagnosed with IRLS criteria</li> <li>• RLS Severity; IRLS&gt;20</li> <li>• baseline score ≥ 15 on the Insomnia severity index (AND)</li> <li>• ≥15 nights of RLS symptoms during the previous month, or if receiving treatment reported they had had symptoms of this frequency before treatment</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• patients with other primary sleep disorders or other clinically relevant conditions affecting assessments</li> <li>• experiencing daytime RLS symptoms that required treatment</li> <li>• experiencing augmentation or end of dose rebound</li> <li>• secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy)</li> <li>• history of alcohol or drug abuse</li> <li>• previous intolerance to dopamine agonists</li> </ul>	<p>N=362</p> <p><b>Age</b> (mean (SD), yr): 55.1</p> <p><b>Gender (Male %):</b> 37%</p> <p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 24.8</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status:</b> NR (secondary RLS de to iron deficiency an exclusion)</p>	<p>score of very much improved or improved (or) at least 50% reduction in IRLS score from baseline</p> <p><b>Adverse Effects Reported:</b> yes</p> <p><b>Intervention</b> Ropinirole (n=147) daily, 1-3 hrs before bedtime. Dose starting at 0.25mg/day and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose</p> <p><b>Comparator:</b> Placebo (n=139)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I scale Score</p> <p><b>B. Quality of life</b> RLS QoL Generic health related quality of life SF-36)</p> <p><b>Subjective Sleep Quality</b> MOS sleep scale</p> <p><b>Definition of clinically significant Improvement:</b> NR</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b> Primary RLS patients with severe disease experiencing night time symptoms and insomnia</p> <p><b>Reviewer Comments Notes</b></p>
<p><b>Study ID</b> Walters, 2004<sup>13</sup></p> <p><b>Geographical Location:</b></p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• age 18 to 79 years</li> <li>• RLS diagnosed with IRLSSG criteria</li> <li>• RLS Severity; IRLS&gt;20</li> </ul>	<p>N=267</p> <p><b>Age</b> (mean (SD), yr): 55.5</p> <p><b>Gender (Male %):</b> 40</p>	<p><b>Intervention</b> Ropinirole (n=131) daily, 1-3 hrs before bedtime Flexible dosing starting at 0.25mg/day up to a maximum of 4mg/day.</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors</p>

<b>Study Characteristics and Design</b>	<b>Inclusion/Exclusion criteria</b>	<b>Participant Characteristics</b>	<b>Intervention (daily dose) /Comparator (daily dose)</b>	<b>Risk of bias and Applicability</b>
<p>International, Multicenter (Australia, Europe, North America)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> Parallel group</p> <p><b>Duration:</b> 12 wks</p>	<ul style="list-style-type: none"> <li>• ≥15 nights of RLS symptoms during the previous month; if patient was undergoing treatment for RLS, then clinician judged whether or not patient would have experienced at least 15 nights of symptoms if they had not been treated</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• experiencing daytime RLS symptoms that required treatment</li> <li>• experiencing augmentation or end of dose rebound with previous medication</li> <li>• secondary RLS (end stage renal disease, iron deficiency anaemia or pregnancy)</li> <li>• other sleep disorders (e.g. narcolepsy, sleep terror disorder, sleep walking disorder, breathing related sleep disorder)</li> <li>• medical conditions that would affect assessment of RLS (e.g., rheumatoid arthritis, fibromyalgia syndrome)</li> <li>• known intolerance to ropinirole</li> <li>• abusing other substances</li> </ul>	<p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 24.2</p> <p><b>Previous RLS medication history:</b> I:48.5%C: 43.4%</p> <p><b>Iron Status:</b> NR</p>	<p><b>Comparator:</b> Placebo (n=136)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I scale Score</p> <p><b>B. Quality of life</b> RLS QoL QoL by SF-36, a generic quality of life instrument</p> <p><b>Subjective Sleep Quality</b> NR</p> <p><b>Definition of clinically significant Improvement:</b> NR</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p>Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments Notes</b></p>

CGI = Clinical Global Impression; IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression; PLMS = periodic leg movements during sleep; SF-36 = Short-Form 36-item Questionnaire

**Appendix C. Table 2. Evidence Table for primary RLS: GABA analogs**

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Study ID</b> Allen, 2010<sup>14</sup></p> <p><b>Anticonvulsant (GABA analog)</b></p> <p><b>Geographical Location:</b> multinational, Europe and US</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> parallel design</p> <p><b>Duration:</b> 12 weeks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>adults, 18 to 65 years of age, meeting diagnostic criteria of the IRLS for idiopathic IRLS (IRLS score <math>\geq 15</math> points, RLS symptoms occurring <math>\geq 15</math> nights between 5 PM and 7 AM disturbing sleep for past 6 months).</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>placebo responders (see reviewer comments), secondary RLS, severe daytime symptoms (requiring treatment), present or past history of another sleep disorder (e.g. sleep apnea)</li> <li>history of failure to respond to gabapentin, serum ferritin <math>&lt; 10 \mu\text{g/L}</math>, failure to have appropriate washout periods for medicines that affect sleep</li> <li>currently on shift work</li> <li>clinically significant liver (bilirubin, aspartate aminotransferase, or alanine aminotransferase levels <math>&gt; 3 \times</math> upper limit of normal) or renal disease (creatinine clearance <math>&lt; 60 \text{ mL/min}</math>)</li> <li>presence of symptomatic neuropathies, severe central nervous system degenerative disease, past or present history of lumbar radiculopathy or central spinal stenosis</li> <li>women who were pregnant, lactating, or of child bearing potential and did not use or</li> </ul>	<p><b>N=137</b></p> <p><b>Age</b> (mean yr): 50.8</p> <p><b>Gender</b> (Male %): 34.3</p> <p><b>Race/Ethnicity</b> (%): NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> <i>See inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 24.8</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status:</b> subjects with serum ferritin <math>&lt; 10 \mu\text{g/L}</math> excluded</p>	<p><b>Intervention:</b> Pregabalin (n=114 total), 5 arms: 50 mg (n=22), 100 mg (n=23), 150 mg (n=22), 300 mg (n=24), 450 mg (n=23)</p> <p><b>Comparator:</b> Placebo (n=23)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score</p> <p><b>B. Quality of life</b> RLS-QoL SF-36</p> <p><b>Subjective Sleep Quality</b> MOS</p> <p><b>Definition of clinically significant Improvement:</b> IRLS responders were patients with <math>\geq 50\%</math> improvement in IRLS total score</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: adequate Allocation concealment: adequate Blinding: patients and personnel Incomplete outcome data: yes, had to have received <math>\geq 1</math> dose of study drug and have <math>\geq 1</math> post-randomization assessment Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b> Placebo responders, defined as having <math>&gt; 50\%</math> improvement in IRLS total score between the beginning of the placebo run-in and baseline were excluded</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Study ID</b> García-Borreguero, 2010<sup>15</sup></p> <p><b>Geographical Location:</b> Spain</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> parallel design, flexible dose</p> <p><b>Duration:</b> 12 weeks</p>	<p>had inadequate contraception.</p> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>adults aged 18–80 years with idiopathic RLS (International Restless Legs Scale [IRLS] total score ≥15 points at baseline) that interfered with sleep onset or sleep maintenance on ≥4 nights/week for at least 6 months</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>secondary RLS</li> <li>coexistence of severe medical or psychiatric disorders</li> <li>previous treatment lasting &gt;12 weeks with DAs, serum ferritin &lt;10 µg/L</li> <li>severe comorbid sleep disorders that might confound assessment</li> <li>shift work.</li> </ul>	<p><b>N</b>=58</p> <p><b>Age</b> (mean yr):</p> <p><b>Gender</b> (Male %):</p> <p><b>Race/Ethnicity</b> (%): white</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS:</b> <i>See inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 20.6</p> <p><b>Previous RLS medication history:</b> 12%</p> <p><b>Iron Status</b> (baseline mean ferritin level, µg/L): 97</p>	<p><b>Intervention:</b> Pregabalin, starting at 150 mg (n=30). Study dose adjustments were performed weekly and were based on clinical judgment of their efficacy and tolerability. The mean daily dosage of pregabalin at the end of treatment was 337.50 mg</p> <p><b>Comparator:</b> Placebo (n=28)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score</p> <p><b>B. Quality of life</b></p> <p><b>Subjective Sleep Quality</b> MOS</p> <p><b>Definition of clinically significant Improvement:</b> IRLS responders were patients with ≥50% improvement in IRLS total score</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding: patients and investigators Incomplete outcome data: no Selective outcome reporting: no</p> <p><b>Reviewer Comments</b> A single-blind placebo run-in was performed. Patients who had a &gt;40% improvement in their IRLS total score during this period were considered placebo responders and excluded from the study.</p>
<p><b>Study ID</b> Kushida, 2009<sup>16</sup></p> <p><b>Geographical Location:</b> USA</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b></p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>adults, aged 18 years or older with a diagnosis of moderate to severe primary RLS using IRLS Study Group diagnostic criteria had RLS symptoms ≥15 days during the month prior to screening (or, if on treatment, similar symptom frequency before treatment initiation) and symptoms on</li> </ul>	<p><b>N</b>=222</p> <p><b>Age</b> (mean yr): 51.1</p> <p><b>Gender</b> (Male %): 40</p> <p><b>Race/Ethnicity</b> (%): white 97</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b></p>	<p><b>Intervention:</b> XP13512 (gabapentin) starting at 1,200 mg (adjusted if AEs present) (n=114)</p> <p><b>Comparator:</b> Placebo (n=108)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI Scale Score</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: adequate Allocation concealment: unclear Blinding: patients and investigators Incomplete outcome data: yes, modified intent-to-treat population (all patients who took at least one dose of study medication and completed a baseline and at least one on-treatment IRLS</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p>parallel design, fixed-dose</p> <p><b>Duration:</b> 12 weeks</p>	<p>≥4 nights during the 7-day baseline period. Prior RLS treatment was discontinued at least 2 weeks prior to baseline. Patients also had an International Restless Legs Scale (IRLS) total score ≥15 at the beginning and end of the baseline period.</p> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• secondary RLS</li> <li>• body mass index ≥34 kg/m<sup>2</sup></li> <li>• were currently experiencing or being treated for moderate to severe depression</li> <li>• other primary sleep disorders, or neurologic disease or movement disorders</li> <li>• history of RLS symptom augmentation or end-of-dose rebound with previous dopaminergic treatment</li> <li>• pregnancy</li> </ul>	<p>IRLSSG</p> <p><b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 22.8</p> <p><b>Previous RLS medication history:</b> 32%</p> <p><b>Iron Status:</b> NR (no secondary RLS)</p>	<p><b>B. Quality of life</b> Johns Hopkins RLS Quality of Life (RLSQoL)</p> <p><b>Subjective Sleep Quality</b> MOS Pittsburgh Sleep Diary</p> <p><b>Definition of clinically significant Improvement:</b> For IRLS total score, response was defined as a six-point decrease from baseline and a score &lt;15.</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>assessment) Selective outcome reporting: no</p>
<p><b>Study ID</b> Garcia-Borreguero 2002<sup>17</sup></p> <p><b>Geographical Location:</b> Spain</p> <p><b>Funding source:</b> Industry (one author an employee of Pfizer)</p> <p><b>Study Design:</b> cross-over, flexible dose</p> <p><b>Duration:</b> two 6-week treatment periods with a 1-week washout period in between</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• criteria for RLS established by the International RLS Study Group</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• ferritin levels below 20 mcg/mL</li> </ul>	<p><b>N=</b>24</p> <p><b>Age</b> (mean yr): 55</p> <p><b>Gender</b> (Male %): 33</p> <p><b>Race/Ethnicity</b> (%): NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> Primary or secondary RLS:</p> <p><b>Baseline Severity:</b> Baseline mean IRLS score: 20</p> <p><b>Previous RLS medication history:</b> None of the patients</p>	<p><b>Intervention:</b> Gabapentin starting at 600 mg daily up to a maximal dose of 2,400 mg/day. The decision to modify the dosage was based on clinical criteria (i.e., therapeutic efficacy and tolerance).</p> <p><b>Comparator:</b> Placebo</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p> <p><b>B. Quality of life</b></p> <p><b>Subjective Sleep Quality</b> Pittsburgh Sleep Quality Index</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding: patients and investigators Incomplete outcome data: no, treatment required Selective outcome reporting: no</p> <p><b>Applicability</b> (Eligibility criterion for inclusion, specific criteria of interest are age, criteria used to define RLS, baseline severity, comorbidities, length of followup)</p> <p><b>Reviewer Comments</b></p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
		<p>had been treated previously with gabapentin or dopaminergic medication.</p> <p><b>Iron Status:</b> Patients with a ferritin value &lt;45 mcg/mL were included in the study and classified as iron deficient. Iron was not administered orally until study completion.</p>	<p><b>Definition of clinically significant Improvement:</b> NR</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>[General comments on quality of reporting, adequateness of statistical analysis]</p>

CGI = Clinical Global Impression; IRLS = International RLS Study Group Rating Scale; MOS = Medical Outcomes Study Sleep Score; NR = not reported; PGI = Patient Global Impression; PLMS = periodic leg movements during sleep; SF-36 = Short-Form 36-item Questionnaire

**Appendix C. Table 3. Evidence Table for primary RLS: Cabergoline trials**

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
<p><b>Study ID</b> Trenkwalder, 2007<sup>18</sup></p> <p><b>Geographical Location</b> Europe (Multicenter)</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> RCT-parallel group</p> <p><b>Duration:</b> 30 wks</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• age 18 to 75 years</li> <li>• RLS diagnosed with IRLSSG criteria</li> <li>• RLS Severity; IRLS&gt;10 and “severity at night” score ≥4 in the 11 point RLS-6 rating scale</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy)</li> <li>• established or suspected hypersensitivity to ergot alkaloids or non-response or intolerability to previous cabergoline or L-dopa therapy</li> <li>• concomitant use of drugs with a probable influence on RLS</li> </ul>	<p><b>N</b>=362</p> <p><b>Age</b> (mean, yr): 57.8</p> <p><b>Gender (Male %):</b> %</p> <p><b>Race/Ethnicity (%):</b> white 100</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Primary or secondary RLS:</b> Idiopathic</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 25.7</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status:</b> NR</p>	<p><b>Intervention:</b> Cabergoline 2-3 mg, 3 hours before bedtime (n=178)</p> <p><b>Comparator:</b> Levodopa 200-300 mg, in 2 doses, the first one 3 hrs before bedtime and the second administered at bedtime (n=183)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score CGI-I scale Score</p> <p><b>B. Quality of life</b> RLS QoL</p> <p><b>Subjective Sleep Quality</b> NR</p> <p><b>Definition of clinically significant Improvement:</b> NR</p> <p><b>Adverse Effects Reported:</b> yes Augmentation assessed using ASRS rating scale</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment</p> <p><b>Selective outcome reporting:</b> no</p> <p><b>Applicability</b> Study population included those with continuous, intermittent and progressive disease</p> <p><b>Reviewer Comments</b> <b>Notes:</b> Patients had to pass a placebo run-in phase of 1 week prior to baseline. 19% of all subjects had augmentation/time shift during previous RLS treatment.</p>
<p><b>Study ID</b> Oertel, 2006<sup>19</sup></p> <p><b>Geographical Location:</b> Europe (Austria, Germany, Norway, Sweden, Netherlands)</p> <p><b>Funding source:</b> Industry</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Age 18-80 yrs</li> <li>• Idiopathic RLS diagnosed with IRLS criteria</li> <li>• Moderate-severe RLS indicated by IRLS scale score&gt;10 ( AND) a RLS severity at night score of 4 or greater on a 11-point RLS-6 rating scale (AND) PLMS arousal index PLMS-AI</li> </ul>	<p><b>N</b>=40</p> <p><b>Age</b> (mean (SD), yr): 56.4</p> <p><b>Gender (Male %):</b> 27</p> <p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p>	<p><b>Intervention</b> Cabergoline (n=20) 2mg/day, once daily, at least 3 hrs before bedtime. Starting dose of 0.5mg/day up titrated to 2.0mg/day over a period of 2 wks.</p> <p><b>Comparator</b> Placebo (n=20)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b></p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug, had a baseline IRLS score and at least 1 post-baseline IRLS assessment</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
<b>Study Design:</b> RCT-Parallel group  <b>Duration:</b> 5 wks	<p>&gt;5per hour total sleep time</p> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Secondary RLS (iron deficiency, renal disease) or drugs suspected to cause such secondary forms</li> <li>• Patients who showed evidence of mimics of RLS</li> <li>• Idiopathic Parkinson disease, insulin-dependent diabetes mellitus, clinically relevant polyneuropathy, liver disease, history of sleep apnea or malignancy, pleural effusions or fibrosis</li> <li>• Established or suspected hypersensitivity to ergot alkaloids</li> <li>• Pretreatment with Cabergoline</li> <li>• Women who were pregnant, or lactating or at risk for pregnancy during course of study</li> </ul>	<p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Primary or secondary RLS:</b> Primary</p> <p><b>Baseline Severity:</b> Severe-very severe. Baseline mean IRLS score: 31.5</p> <p><b>Previous RLS medication history:</b> Patients with previous RLS treatment I:95% C:80%</p> <p><b>Iron Status:</b> NR</p>	<p>IRLS Scale Score</p> <p><b>B. Quality of life</b> QoL RLS</p> <p><b>Subjective Sleep Quality</b> NR (Study only reports a subscale of SF-A)</p> <p><b>Definition of clinically significant Improvement:</b> Responders defined as patients with at least 50% reduction of their baseline IRLS score or those who assessed their condition at week 6 as “much better” or “very much better” on patient global impressions scale</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p>Selective outcome reporting: no</p> <p><b>Applicability</b> Study participant had severe RLS, severe night time symptom scores and periodic limb movements of sleep</p> <p><b>Reviewer Comments</b> Not ITT. Randomized=345; Analyzed=338</p> <p><b>Notes:</b> 63% of all subjects had drug-related augmentation during previous RLS treatment.</p>
<p><b>Study ID</b> Stiasny-Kolster, 2004<sup>20</sup></p> <p><b>Geographical Location:</b> Germany, Multicenter</p> <p><b>Funding source:</b> Industry and Govt.</p> <p><b>Study Design:</b> RCT-Parallel group Dose-ranging study with 3 different intervention arms</p> <p><b>Duration:</b></p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Age 18-75 yrs</li> <li>• Idiopathic RLS diagnosed with IRLS criteria</li> <li>• RLS Severity; IRLS&gt;15 and a RLS severity at night≥4 on 11 point RLS-6 scale</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Patients with uremia, iron deficiency and rheumatoid arthritis</li> <li>• Patients with idiopathic Parkinson’s syndrome, insulin-dependent diabetes, polyneuropathy, liver</li> </ul>	<p><b>N=86</b></p> <p><b>Age</b> (mean, yr): 56.1</p> <p><b>Gender (Male %):</b> 30%</p> <p><b>Race/Ethnicity (%):</b> NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b> IRLSSG diagnostic criteria</p> <p><b>Primary or secondary RLS:</b></p>	<p><b>Intervention:</b> Cabergoline in 3 different doses: 0.5 mg/day (n=21); 1.0 mg/day (n=20); and 2.0 mg/day (n=22)</p> <p><b>Comparator:</b> Placebo (n=22)</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p> <p><b>B. Quality of life</b> NR</p> <p><b>Subjective Sleep Quality</b></p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, “7 withdrawn from study as they fulfilled definition of non-responders”; To be included in the analysis patients had to have at least 1 assessment.</p> <p><b>Selective outcome reporting:</b> no</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
5 wks	<p>disease, history of sleep apnea, malignancy, pleural effusions or fibrosis, and established or suspected hypersensitivity to ergot alkaloids</p> <ul style="list-style-type: none"> <li>• Women who were pregnant, at risk for pregnancy or lactating</li> <li>• Concomitant medications that influence sleep architecture or motor manifestations during sleep within the last week before baseline visit and during the trial. These include: neuroleptics, dopamine agonists, L-dopa, hypnotics, antidepressants, anxiolytics, anticonvulsants, psychostimulant medications and opioids.</li> </ul>	<p>Primary</p> <p><b>Baseline Severity:</b> Moderate-Severe. Baseline mean IRLS score: 26.6</p> <p><b>Previous RLS medication history:</b> Patients with previous RLS treatment 63.5%</p> <p><b>Iron Status:</b> NR</p>	<p>NR (Sleep diaries were used to document quality and duration of sleep; but they did not use a validated sleep scale)</p> <p><b>Definition of clinically significant Improvement:</b> Remitters defined as those IRLS scale score=0</p> <p><b>Adverse Effects Reported:</b> yes</p>	<p><b>Applicability</b></p> <p><b>Reviewer Comments</b></p> <p>Not strictly ITT. Randomized=86; Analyzed=8</p> <p><b>Notes</b></p>

IRLS = International RLS Study Group Rating Scale; NR = not reported

**Appendix C. Table 4. Evidence Table for secondary RLS: iron trials**

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
<p><b>Study ID</b> Grote, 2009<sup>21</sup></p> <p><b>Geographical Location:</b> Sweden</p> <p><b>Funding source:</b> Industry</p> <p><b>Study Design:</b> parallel design, fixed dose</p> <p><b>Duration:</b> 12 months</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• age between 18 and 70 years</li> <li>• 4 cardinal RLS diagnostic criteria*</li> <li>• score of ≥10 on the IRLS</li> <li>• S-ferritin concentration &lt;30 µg/L. A study amendment issued after inclusion of 30 patients increased the threshold for S-ferritin to 45 µg/L according to previously published recommendations</li> <li>• normal folic acid/ B12 vitamin serum values.</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• concomitant use of any drug treatment for RLS</li> <li>• clinical or laboratory findings suggestive of secondary RLS</li> <li>• any previously known clinically significant allergic reaction</li> <li>• use of drug treatment known to induce RLS</li> <li>• pregnancy</li> <li>• specific contraindication for iron sucrose</li> </ul>	<p><b>N</b>=60</p> <p><b>Age</b> (mean yr): 46.5</p> <p><b>Gender</b> (Male %): 12</p> <p><b>Race/Ethnicity</b> (%): NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS:</b> <i>see inclusion criteria</i></p> <p><b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 24.6</p> <p><b>Previous RLS medication history:</b> NR</p> <p><b>Iron Status</b> (serum ferritin (µg/L)): 20.55</p>	<p><b>Intervention:</b> Intravenous iron sucrose 200 mg x 5 occasions over 3 weeks (n=29)</p> <p><b>Comparator:</b> Placebo (intravenous saline) (n=31)</p> <p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p> <p><b>B. Quality of life</b> NR</p> <p><b>Subjective Sleep Quality</b> Epworth Sleepiness Scale</p> <p><b>Definition of clinically significant Improvement:</b> responders had ≥50% IRLS score reduction (A post-hoc analysis)</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding: patients and investigators Incomplete outcome data: no Selective outcome reporting: no</p>
<p><b>Study ID</b> Wang, 2009<sup>22</sup></p> <p><b>Geographical Location:</b> Europe (43 hospitals and sleep clinics in: Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK)</p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• RLS diagnosed with IRLS criteria*</li> <li>• RLS Severity; IRLS ≥11 (AND) measured ferritin level of 15-7 5ng/ml</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• pregnancy</li> <li>• hemochromatosis, or other significant liver disease, end-stage renal disease or significant sleep disturbance</li> </ul>	<p><b>N</b>=18</p> <p><b>Age</b> (mean (SD), yr): 59.2</p> <p><b>Gender</b> (Male %): 39%</p> <p><b>Race/Ethnicity</b> (%): NR</p> <p><b>Comorbidities:</b> NR</p> <p><b>Criteria used to define RLS</b></p>	<p><b>Intervention:</b> Oral ferrous sulfate 650 mg (n=11)</p> <p><b>Comparator:</b> Placebo (n=7)</p> <p>All patients were also asked to take vitamin C 100 mg twice daily.</p> <p><b>Outcomes reported:</b> <b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p>	<p><b>Assessment of Internal Validity</b> Sequence generation: yes Allocation concealment: yes Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: no Selective outcome reporting: no</p> <p><b>Reviewer Comments</b> <b>Notes.</b> Performed at Veterans</p>

<b>Study Characteristics and Design</b>	<b>Inclusion/Exclusion criteria</b>	<b>Participant Characteristics</b>	<b>Intervention (daily dose) /Comparator (daily dose)</b>	<b>Risk of bias and Applicability</b>
<b>Funding source:</b> Industry  <b>Study Design:</b> Parallel group  <b>Duration:</b> 12 wks	for reasons other than RLS <ul style="list-style-type: none"> <li>• iron saturation less than 15%</li> <li>• iron sulphate allergy</li> <li>• hemoglobin levels less than 11.1 g/dL for females and 14g/dL for male</li> <li>• current or recent treatment with iron sulfate as defined by more than 325 mg each day for at least half of the days in the past 2 months or any other potential medications for treatment of RLS.</li> </ul>	IRLSSG diagnostic criteria  <b>Baseline Severity:</b> moderate to severe. Baseline mean IRLS score: 24.1  <b>Previous RLS medication history:</b> NR  <b>Iron Status:</b> NR	<b>B. Quality of life</b> NR  <b>Subjective Sleep Quality</b> NR  <b>Definition of clinically significant Improvement:</b> NR  <b>Adverse Effects Reported:</b> yes	Affairs Medical Center, included active duty personnel, retirees, or family members

IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression

\* The 4 critical criteria are: 1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs); 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; 3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking stretching, at least as long as the activity continues; 4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

**Appendix C. Table 5. Evidence Table for the nonpharmacologic studies**

<b>Study Characteristics and Design</b>	<b>Inclusion/Exclusion criteria</b>	<b>Participant Characteristics</b>	<b>Intervention (daily dose) /Comparator (daily dose)</b>	<b>Study Quality and Applicability</b>
<p>Cuellar, 2009<sup>23</sup></p> <p><b>Botanical preparation</b></p> <p>Geographical Location: US</p> <p>Funding source: NR</p> <p>Study Design: parallel design</p> <p>Duration: 8 weeks</p>	<p>Inclusion criteria: Met diagnostic criteria based on the IRLS criteria including akathisia brought on by rest, relieved with moving or walking, and worsening at night or in the evening; at least 21 years old; not satisfied with current treatment outcomes; willing to use valerian as treatment with possibility of being in control group; have symptoms of RLS 3 nights a week or more; commitment to treatment fidelity.</p> <p>Exclusion criteria: Positive toxicology report, liver function profile abnormal, and 3 yes answers on CAGE 2; participation in a clinical study with an investigation drug within 3 months; current use of vitamins or minerals beyond the recommended RDA requirements; current use of any herbs or natural products; current use of benzodiazepines or barbiturates; sleep disorder other than RLS; use of valerian within 120 days of baseline visit; history of liver disease including cirrhosis, alcoholism, and hepatitis; pregnant, nursing, or intending to become pregnant in 3 months.</p>	<p>N=48</p> <p>Age (mean yr): 49.5</p> <p>Gender (Male %): 25</p> <p>Race/Ethnicity (%): white 68</p> <p>Comorbidities: NR</p> <p><b>Criteria used to define RLS</b></p> <p>Primary or secondary RLS:</p> <p>Baseline Severity: IRLSS 23.5</p> <p>Previous RLS medication history: yes</p> <p>Iron Status: NR</p>	<p>Valerian 800 mg (n=24)</p> <p>Placebo (identical in taste, color, etc.) (n=24)</p> <p><b>A. Change in Disease Status and Impact</b></p> <p>IRLS Scale Score</p> <p><b>B. Quality of life</b></p> <p>None</p> <p><b>Subjective Sleep Quality</b></p> <p>Pittsburgh Sleep Quality Index (PSQI)</p> <p>Epworth Sleepiness Scale (ESS)</p> <p><b>Definition of clinically significant Improvement:</b> none provided</p> <p><b>Adverse Effects Reported:</b> Yes</p>	<p><b>Assessment of Internal Validity</b></p> <p>Sequence generation: adequate</p> <p>Allocation concealment: adequate, pharmacy controlled</p> <p>Blinding: patients, personnel, data enterer, outcome assessment</p> <p>Incomplete outcome data: yes, needed to take at least one dose of study medication</p> <p>Selective outcome reporting: No</p> <p>Applicability</p> <p>Yes</p> <p>Reviewer Comments</p> <p>None</p>
<p>Lettieri, 2009<sup>24</sup></p> <p><b>Compression device</b></p>	<p>Inclusion criteria: patients presenting to the sleep clinic for evaluation of RLS were approached for participation;</p>	<p>N=35</p> <p>Age (mean yr): 51.0</p>	<p>Compression device (n=21)</p> <p>Control (n=14)</p>	<p><b>Assessment of Internal Validity</b></p> <p>Sequence generation: adequate</p> <p>Allocation concealment: adequate</p> <p>Blinding: patients, physicians,</p>

<b>Study Characteristics and Design</b>	<b>Inclusion/Exclusion criteria</b>	<b>Participant Characteristics</b>	<b>Intervention (daily dose) /Comparator (daily dose)</b>	<b>Study Quality and Applicability</b>
<p>Geographical Location: US</p> <p>Funding source: NR</p> <p>Study Design: Prospective, randomized, double-blind, sham-controlled trial</p> <p>Duration: 28 days</p>	<p>subjects &gt; 17 years old with a reliable diagnosis of RLS in accordance with the <i>International Classification of Sleep Disorders, Revised Diagnostic and Coding Manual</i> of the American Academy of Sleep Medicine</p> <p>Exclusion criteria: individuals &lt; 17 years old; those with mental or physical limitations that would preclude data collection on questionnaires; and those with medical conditions that would preclude the use of PCDs, such as known or suspected deep vein thrombosis, active skin infections, recent vein ligation or skin graft, or extreme deformity of the legs. We also excluded individuals if they had previously used PCDs for deep vein thrombosis prophylaxis, as this would have potentially unblinded subjects randomized to sham devices.</p>	<p>Gender (Male %): 60</p> <p>Race/Ethnicity (%): NR</p> <p>Comorbidities: NR</p> <p><b>Criteria used to define RLS</b> see inclusion criteria</p> <p>Baseline Severity: IRLS 19.8</p> <p>Previous RLS medication history: Subjects taking iron or prescription medications for RLS were offered enrollment only if they had been on a stable dose of medications for more than two months and reported persistent symptoms.</p> <p>Iron Status: Current iron therapy 17.1%</p>	<p><b>A. Change in Disease Status and Impact</b> IRLS Scale Score</p> <p><b>B. Quality of life</b> Yes</p> <p><b>Subjective Sleep Quality</b> Yes</p> <p><b>Definition of clinically significant Improvement:</b> No</p> <p><b>Adverse Effects Reported:</b> Yes</p>	<p>investigators</p> <p>Incomplete outcome data: adequate</p> <p>Selective outcome reporting: no</p> <p>Reviewer Comments None</p>
<p>Aukerman, 2006<sup>25</sup></p> <p><b>Exercise</b></p> <p>Geographical Location: US</p> <p>Funding source: non-industry</p> <p>Study Design: parallel design</p>	<p>Inclusion criteria: meeting diagnostic criteria for RLS, no secondary causes of RLS</p> <p>Exclusion criteria: orthopedic condition that limited ambulation on a treadmill or ability to perform prescribed resistance exercises, recent coronary event in the preceding six months, uncontrolled hypertension, renal dysfunction (serum creatinine &gt;1.5 mg/dL) or anemia (hemoglobin &lt;13</p>	<p>N=41, demographic data for 28 subjects who completed trial (9 exercise and 4 controls dropped out)</p> <p>Age (mean yr): 53.7</p> <p>Gender (Male %): 39</p> <p>Race/Ethnicity (%): white 96</p> <p>Comorbidities: NR</p> <p><b>Criteria used to define RLS</b></p>	<p>Exercise (lower body resistance exercises performed 3 times/week for 12 weeks and treadmill walking for aerobic exercise) (n=11)</p> <p>Control (n=17)</p> <p>Both groups were instructed in lifestyle interventions that are thought to improve RLS, including cigarette and alcohol cessation, avoidance of excessive caffeine, and proper sleep hygiene.</p>	<p><b>Assessment of Internal Validity</b></p> <p>Sequence generation: adequate</p> <p>Allocation concealment: unclear</p> <p>Blinding: study personnel blinded to allocation called participants at 3 and 9 weeks to complete the questionnaire over the phone</p> <p>Incomplete outcome data: yes</p> <p>Selective outcome reporting: no</p> <p>Applicability Yes</p> <p>Reviewer Comments</p>

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Study Quality and Applicability
Duration: 12 weeks	g/dL in males and <11 g/dL in females).	Primary or secondary RLS: primary  Baseline Severity: NR  Previous RLS medication history: NR  Iron Status: NR	<b>A. Change in Disease Status and Impact</b> IRLS Scale Score  <b>B. Quality of life</b> None  <b>Subjective Sleep Quality</b> No  <b>Definition of clinically significant Improvement:</b> none provided  <b>Adverse Effects Reported:</b> yes	None

IRLS = International RLS Study Group Rating Scale; NR = not reported

# **Appendix D**

**Appendix D. Table 1. IRLS responders ( $\geq 50\%$  score reduction) at end of treatment for the dopamine agonist studies**

Study, year	Duration (weeks)	Drug and daily dosage / control	Positive response % (n/N)	Risk ratio [95% CI]
Montagna, 2011 <sup>2</sup>	12	Pramipexole 0.125-0.75 mg	75.9 (154/203)	1.32 [1.15 to 1.53]
		Placebo	57.3 (114/199)	
Oertel, 2007 <sup>7</sup>	6	Pramipexole 0.125-0.75 mg	52.2 (117/224)	1.80 [1.32 to 2.47]
		Placebo	28.9 (33/114)	
Winkelman, 2006 <sup>11</sup>	12	Pramipexole 0.125-0.75 mg	61.8 (157/254)	1.46 [1.12 to 1.90]
		Placebo	42.4 (36/85)	
Hening, 2010 <sup>26</sup>	26	Rotigotine 0.5,1,2,3 mg	56.9 (224/394)	1.52 [1.16 to 1.99]
		Placebo	37.4 (37/99)	
Oertel, 2010 <sup>27</sup>	7	Rotigotine 1-3 mg	76.1 (35/46)	2.17 [1.17 to 4.04]
		Placebo	35.0 (7/20)	
Trenkwalder, 2008 <sup>6</sup>	29	Rotigotine 1-3 mg	55.0 (183/333)	2.16 [1.55 to 3.00]
		Placebo	25.4 (29/114)	

CI = confidence intervals; IRLS = International Restless Legs Study Group Rating Scale.

**Appendix D. Table 2. International Restless Legs Study Group Rating Scale (IRLS) scores for the dopamine agonist studies**

Author year	Study Duration (weeks)	Intervention/Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value
Högl, 2011 <sup>1</sup>	26	Pramipexole (0.125-0.75 mg) (166)	23.9 (5.3)	10.2	-13.7 (0.8)	-3.7	0.0077
		Placebo (163)	23.5 (5.4)	12.4	-11.1 (0.8)		
Montagna, 2011 <sup>2</sup>	12	Pramipexole (0.125-0.75 mg) (203)	25.9 (5.2)	11.4 (9.2)	-14.2 (0.7)	-6.1 [-4.3 to -7.9]	< 0.0001
		Placebo (200)	25.9 (5.5)	17.4 (10.4)	-8.1 (0.7)		
Oertel, 2010 <sup>27</sup>	4	Rotigotine (1-3 mg) (46)	26.3 (6.4)	9.7 (9.1)	-16.5 (9.3)	-6.09 [-10.71 to 1.47]	0.0107
		Placebo (21)	25.4 (6.3)	-	-9.9 (9.9)		
Ferini-Stambi, 2008 <sup>4</sup>	12	Pramipexole (0.25-0.75 mg) (182)	24.3 (5.1)	10.8 (9.1)	-13.4 (0.7)	-3.8	< 0.0001
		Placebo (187)	24.6 (5.8)	15.0 (10.9)	-9.6 (0.7)		
Kushida, 2008 <sup>5</sup>	12	Ropinirole (0.5-6.0 mg) (176)	-	-	~ -11 (3)*	-4.11 [-6.08 to -2.14]	0.001
		Placebo (186)	-	-	~ -15.5 (3)*		
Trenkwalder, 2008 <sup>6</sup>	24	Rotigotine (1 mg) (115)	28.1 (6.3)	-	-13.7 (0.9)	-5.1 [-7.6 to -2.7]	< 0.0001
		Rotigotine (2 mg) (112)	28.2 (6.1)	-	-16.2 (0.9)	-7.5 [-10.0 to -5.1]	< 0.0001
		Rotigotine (3 mg) (114)	28.0 (5.9)	-	-16.8 (0.9)	-8.2 [-10.6 to -5.7]	< 0.0001
		Placebo (117)	28.1 (6.3)	-	-8.6 (0.9)		
Oertel, 2007 <sup>7</sup>	6	Pramipexole (0.125-0.750 mg) (230)	24.7 (5.2)	12.3 (9.3)	-12.3 (0.6)	-6.6 [-8.6 to -4.5]	< 0.0001
		Placebo (115)	24.9 (5.4)	18.8 (10.0)	-5.7 (0.9)		
Bogan, 2006 <sup>9</sup>	12	Ropinirole (0.25-4.00 mg) (187)	22.0 (4.99)	8.4 (7.32)	-13.5 (1.2)	-3.7 [-5.4 to -2.0]	< 0.001
		Placebo (194)	21.6 (4.79)	11.9 (9.20)	-9.8 (1.2)		
Montplaisir, 2006 <sup>10</sup>	12	Ropinirole (mean 2.05 mg) (45)	8.9 (7.41)	-	4.1	-4.6 [-8.6 to -0.6]	0.0246
		Placebo (47)	10.4 (7.30)	-	8.2		
Winkelman, 2006 <sup>11</sup>	12	Pramipexole (0.25 mg) (88)	23.4 (4.9)	-	-12.8 (1.0)	-	0.0086
		Pramipexole (0.50 mg) (80)	22.9 (5.1)	-	-13.8 (1.0)	-	0.0011
		Pramipexole (0.75 mg) (90)	24.1 (5.2)	-	-14.0 (1.0)	-	0.0005
		Placebo (86)	23.5 (5.2)	-	-9.3 (1.0)		

Author year	Study Duration (weeks)	Intervention/Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value
Adler, 2004 <sup>8</sup>	5	Ropinirole (0.5-6.0 mg) (11) Placebo (11)	(overall) 25.0 (7.0)	13.0 (12.0) 24.7 (7.2)	-12.0 (12.0) -	-12.0 [-17.0 to -6.3]	< 0.001
Trenkwalder, 2004 <sup>12</sup>	12	Ropinirole (0.25-4.00 mg) (147) Placebo (139)	24.4 (5.75) 25.2 (5.63)	13.5 (9.3) 17.1 (9.4)	-11.04 (0.72) -8.03 (0.74)	-3.01 [-5.03 to -0.99]	0.0036
Walters, 200 <sup>13,4</sup>	12	Ropinirole (0.25-4.0 mg) (131) Placebo (136)	23.6 (5.9) 24.8 (5.4)	- -	-11.2 (0.76) -8.7 (0.75)	-2.5 [-4.6 to -0.4]	0.0197

CI = confidence interval; SE = standard error; SD = standard deviation; mg = milligrams; \*estimated from table.

**Appendix D. Table 3. International Restless Legs Study Group Rating Scale (IRLS) scores for GABA analog studies**

Author year	Study Duration (weeks)	Intervention/ Comparator, daily dose (n)	IRLS score (SD), Baseline	IRLS score (SD), After treatment	Before/After Difference (SD)	Treatment versus Control, Difference [95% CI]	p-value vs. control
Allen, 2010 <sup>14</sup>	6	Pregabalin 50 mg (22)	24.6 (6.7)	-	-11.9 (10.9)	-4.20 [-9.75 to 1.35]	NS*
		Pregabalin 100 mg (23)	25.3 (6.4)	-	-12.3 (9.0)	-4.60 [-9.30 to 0.10]	NS*
		Pregabalin 150 mg (22)	26.2 (7.4)	-	-17.2 (10.3)	-9.50 [-15.03 to -3.79]	<0.05*
		Pregabalin 300 mg (24)	25.0 (7.4)	-	-12.6 (8.6)	-4.90 [-9.41 to -0.39]	<0.05*
		Pregabalin 450 mg (23)	24.1 (7.8)	-	-15.6 (9.0)	-7.90 [-12.75 to -3.05]	<0.05*
		Placebo (23)	23.8 (7.2)	-	-7.7 (6.6)	-	-
Garcia-Borreguero, 2010 <sup>15</sup>	12	Pregabalin 150-450 mg (30)	19.80 (4.16)	6.85 (6.87)		-4.92 [0.73 to 9.12]**	0.005
		Placebo (28)	21.46 (3.81)	11.2 (8.60)			-
Kushida, 2009 <sup>16</sup>	12	Gabapentin (XP13512/ GSK1838262) 1200 mg (114)	23.1 (4.9)	-	-13.2 (9.2)	-4.0 [-6.2 to -1.9]**	0.0003
		Placebo (108)	22.6 (4.9)	-	-8.8 (8.6)		
Garcia-Borreguero, 2002 <sup>17</sup>	6	Gabapentin 600-2400 mg (22)	20.0 (all subjects)	9.5 (1.35)	-	-8.40 [-12.06 to -4.74]	< 0.001
		Placebo (22)		17.9 (1.35)	-		

CI = confidence intervals; SE = standard error; SD = standard deviation; mU = mouse units.

\* Based on confidence intervals

\*\* adjusted

**Appendix D. Table 4. International Restless Legs Study Group Rating Scale (IRLS) scores for the cabergoline studies**

Author year	Study Duration (weeks)	Intervention/Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SD/SE)	Treatment versus Control, Difference [95% CI]	p-value
Trenkwalder, 2007 <sup>18</sup>	30	Cabergoline (2/3 mg) (178)	25.6 (7.2)	-	-15.6 (10.8)	-7.0 [-9.1 to -4.9]	<0.001
		Levodopa (200/300 mg) (183)	25.8 (6.2)	-	-8.8 (10.7)		
Oertel, 2006 <sup>19</sup>	5	Cabergoline (2 mg) (20)	31.2 (5.4)	-	-23.7 (11.2)	-15.8 [-22.68 to -8.92]	<0.001
		Placebo (20)	31.8 (4.0)	-	-7.9 (11.0)		
Stiasny-Kolster, 2004 <sup>20</sup>	47	Cabergoline (0.5 mg) (21)	27.2 (5.1)	-	-13.1 (10.3)	-9.8 [-15.33 to 4.27]	<0.001
		Cabergoline (1.0 mg) (20)	25.2 (4.5)	-	-13.5 (9.9)		
		Cabergoline (2.0 mg) (22)	27.7 (5.7)	-	-15.7 (11.9)		
		Placebo (22)	26.0 (5.5)	-	-3.3 (8.0)		

CI = confidence interval; SE = standard error; SD = standard deviation; mg = milligrams; \*estimated from table.

**Appendix D. Table 5. International Restless Legs Study Group Rating (IRLS) scores for nonpharmacologic studies**

Author, year	Study Duration (weeks)	Intervention/Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SD/SE)	Treatment versus Control, Difference [95% CI]	p-value
Cuellar, 2009 <sup>28</sup>	8	Valerian (800 mg) (24)	23.0 (5.9)	--	3.4 (9.4)	-1.30 [-7.68, 5.08]	0.69
		Placebo (NR) (24)	24.0 (8.0)	--	4.7 (10.4)		
Lettieri, 2008 <sup>24</sup>	4	Compression (21)	20.3 (5.9)	8.4 (3.4)	--	-5.70 [-8.21, -3.19]	P < 0.05
		Sham (14)	19.0 (5.2)	14.1 (3.9)	--		
Aukerman, 2006 <sup>25</sup>	12	Exercise (11)	20.6 (6.4)	12.1 (5.6)	--	-9.40 [-13.86, -4.94]	P < 0.05
		Control (17)	22.5 (6.4)	21.5 (6.3)	--		

**Appendix D. Table 6. International Restless Legs Study Group Rating Scale (IRLS) scores for iron studies**

Author year	Study Duration (weeks)	Intervention (n) / Comparator (n)	IRLS score (SD), Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value vs. control
Grote, 2009 <sup>21</sup>	52	Iron sucrose 200 mg x 5 times over three months I.V. (29)	23.2 (6.6)	14.6 (10.6)	-8.7 (9.4)	-1.80 [-6.63 to 3.03]	0.47
		Placebo (31)	25.9 (5.6)	19.0 (9.4)	-6.9 (9.7)		
Wang, 2009 <sup>22</sup>	12	Oral iron 650 mg (7)	24.8 (5.72)	-	-10.3 (7.40)	-9.16 [-15.21 to -3.11]	0.01
		Placebo (11)	23.0 (5.03)	-	-1.14 (5.64)		

CI = confidence intervals; IV = intravenously; SE = standard error; SD = standard deviation; mU = mouse units; \*10-item IRLS.

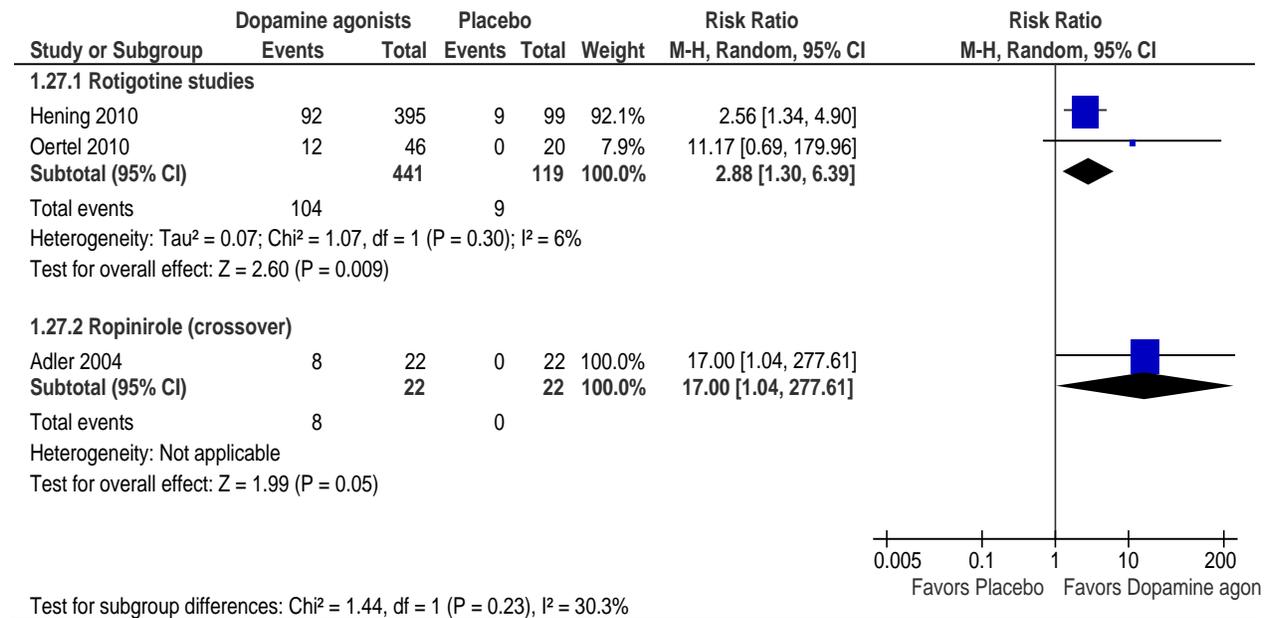
**Appendix D. Table 7. IRLS Remitters (score = 0): Absolute effect per 100 patients**

<b>Study</b>	<b>Number of studies</b>	<b>Dopamine Agonist % (n/N)</b>	<b>Placebo % (n/N)</b>	<b>RR [95% CI]</b>	<b>Absolute effect [95% CI]</b>
Rotigotine	2	23.6 (104/441)	7.6 (9/119)	2.88 [1.30 to 6.39]	14 more per 100 [2 more to 41 more]

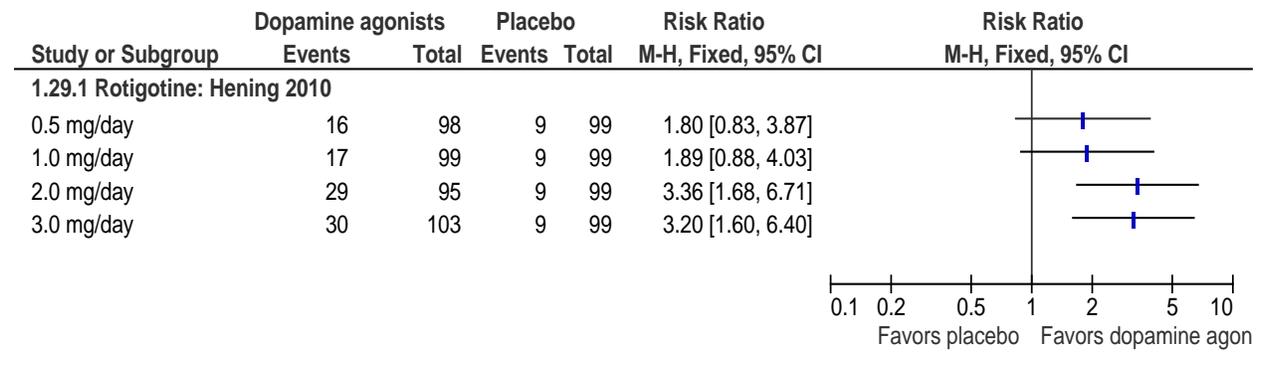
CI = confidence intervals.

## Appendix D. Figure 1. IRLS Remitters analyses

### IRLS Remitters (score = 0)

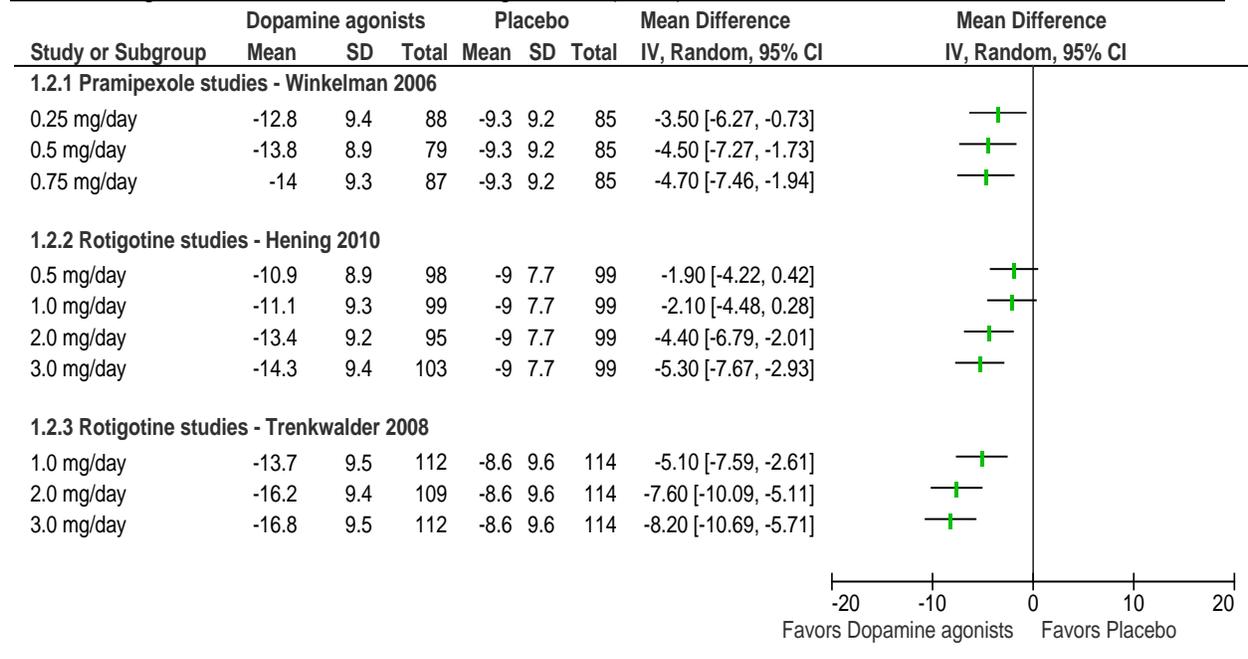


### IRLS Remitters (score = 0): Fixed dose analyses

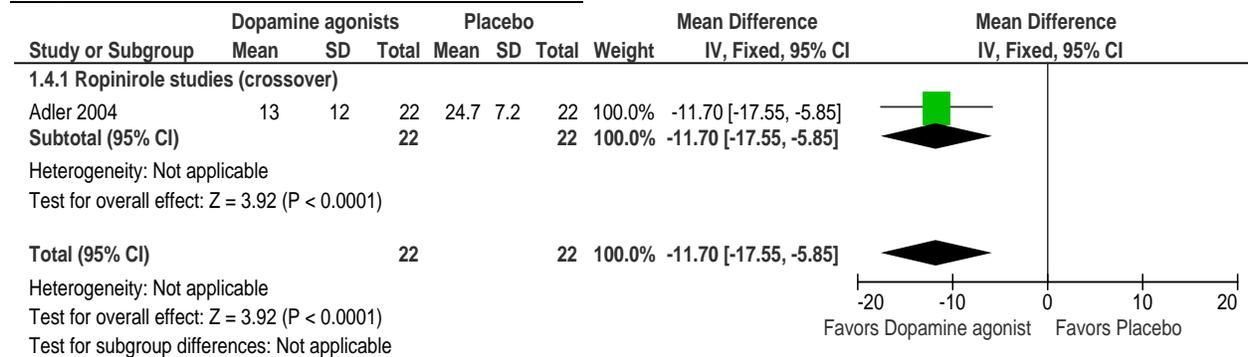


**Appendix D. Figure 2. Efficacy and Harms data for double-blind dopamine agonist trials**

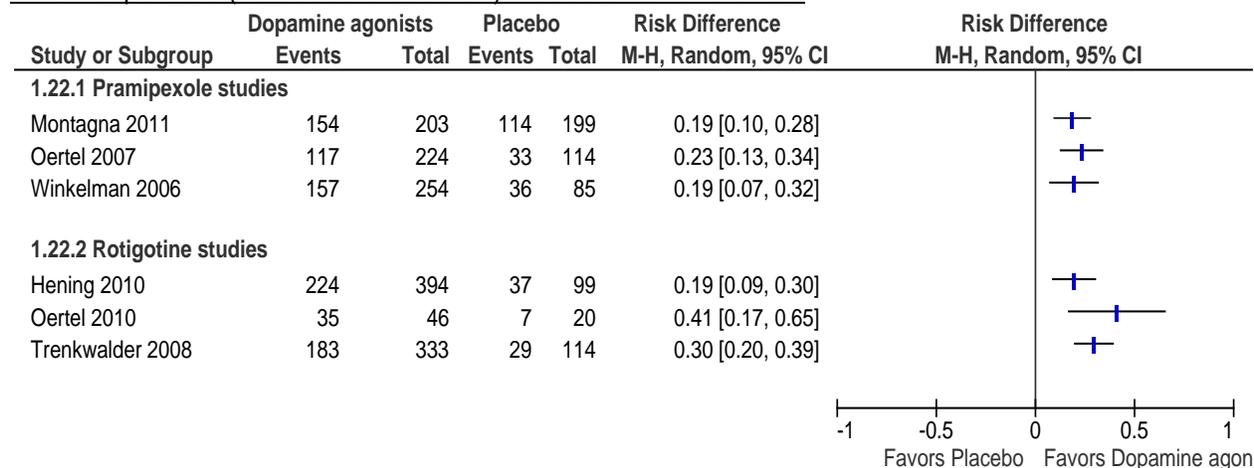
Mean change in International Restless Legs Scale (IRLS) total score from baseline – fixed-dose studies



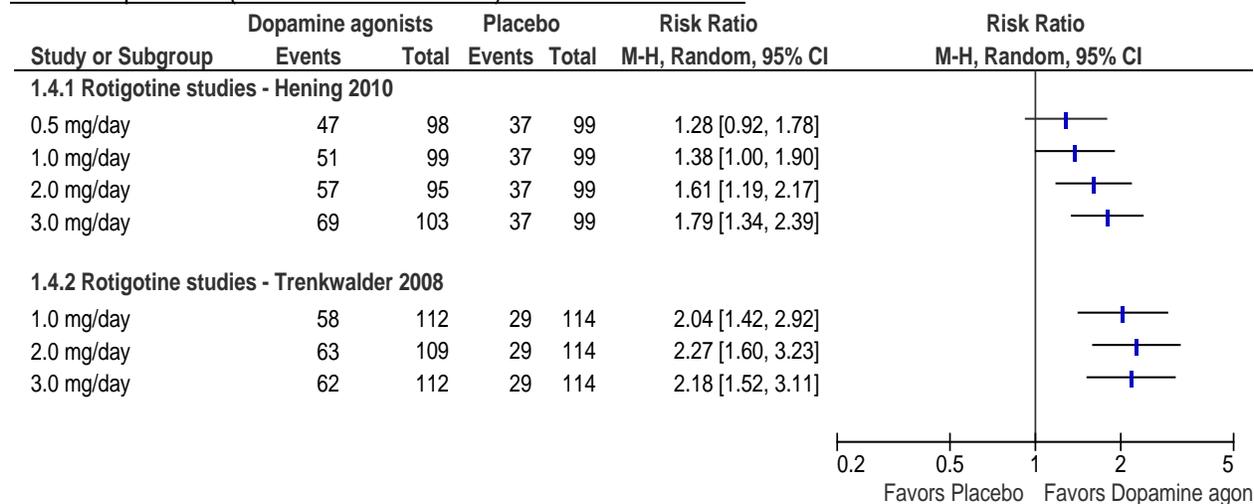
IRLS total score: mean score at end of treatment



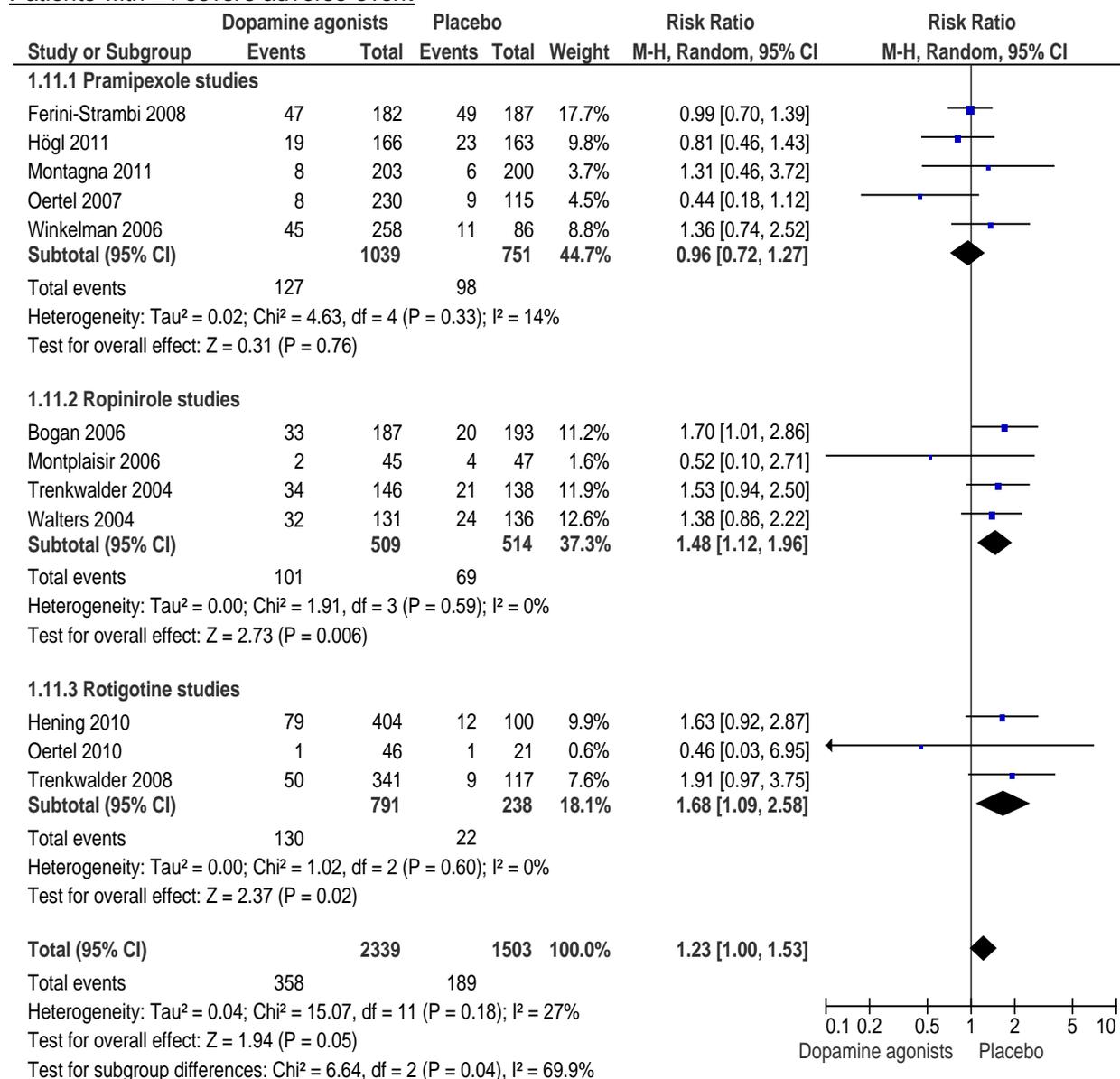
**IRLS Responders ( $\geq 50\%$  score reduction): Absolute risk differences**



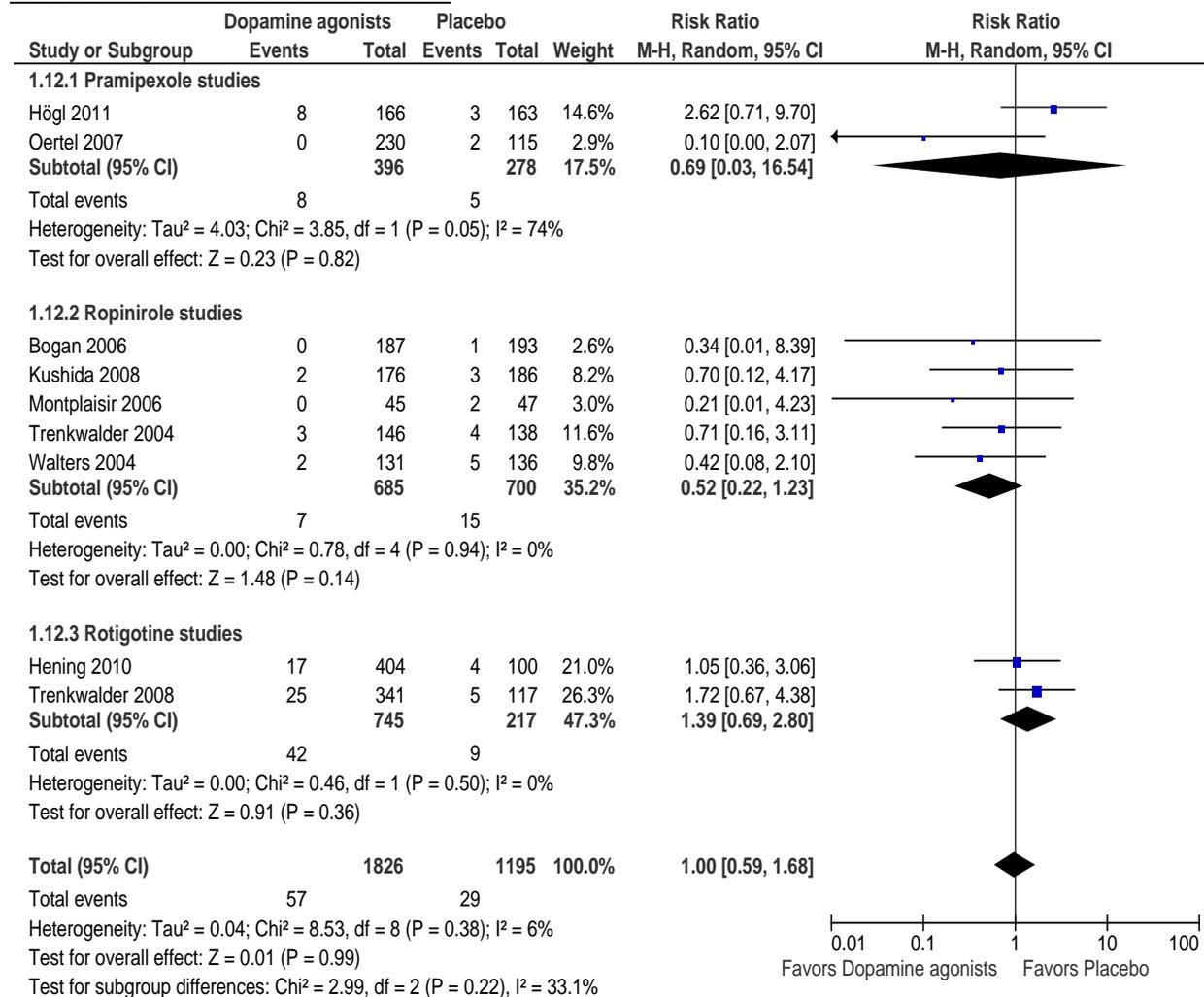
**IRLS Responders ( $\geq 50\%$  score reduction) – fixed-dose studies**



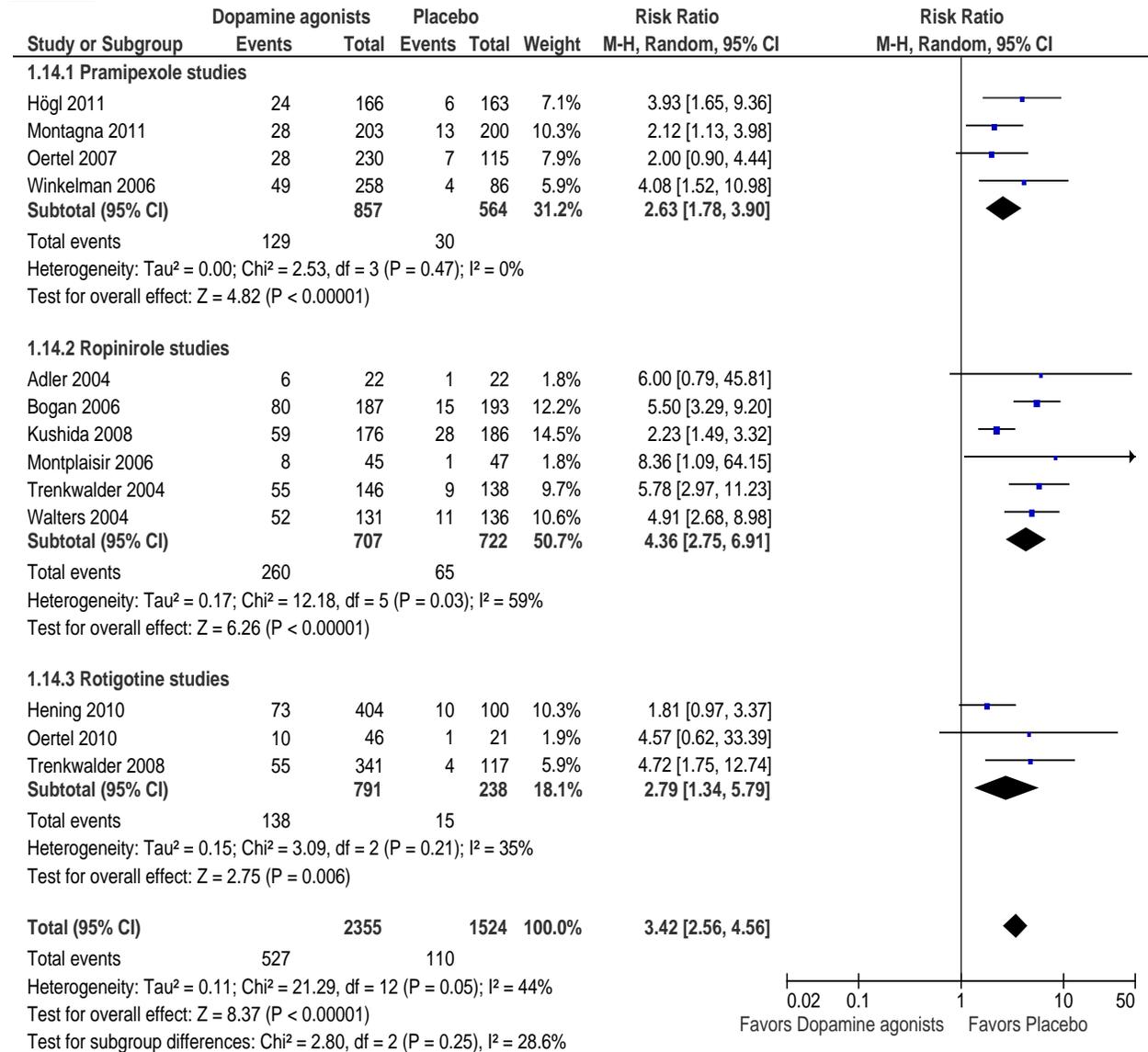
**Patients with  $\geq 1$  severe adverse event**



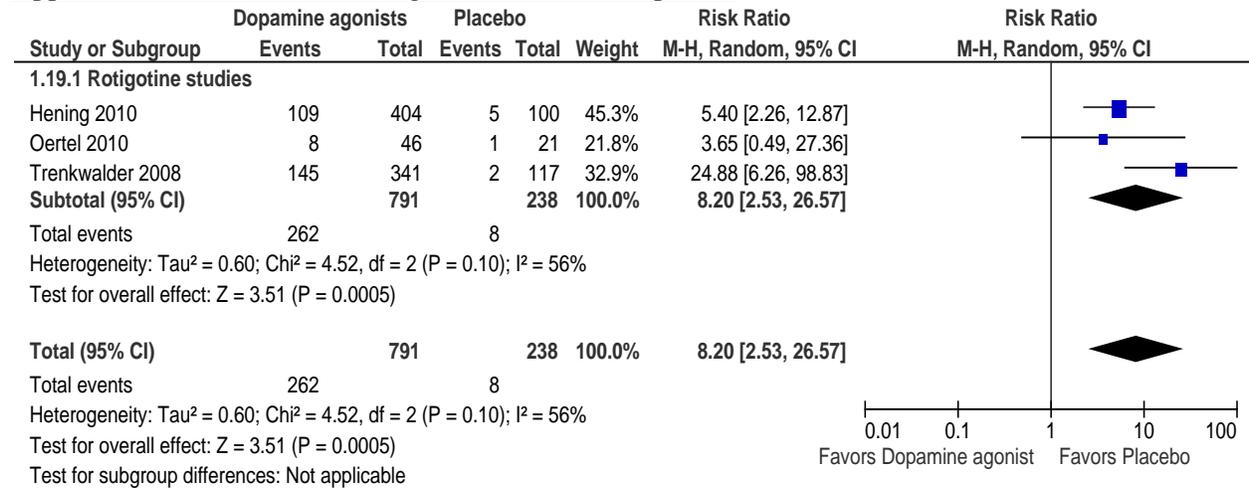
**Patients with  $\geq 1$  serious adverse event**



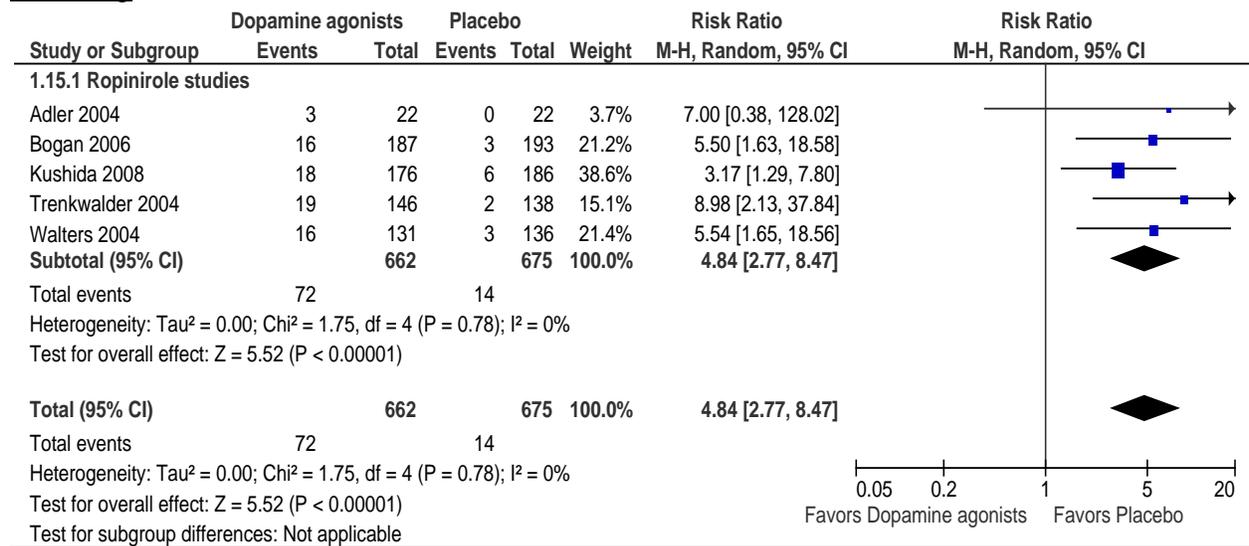
## Nausea



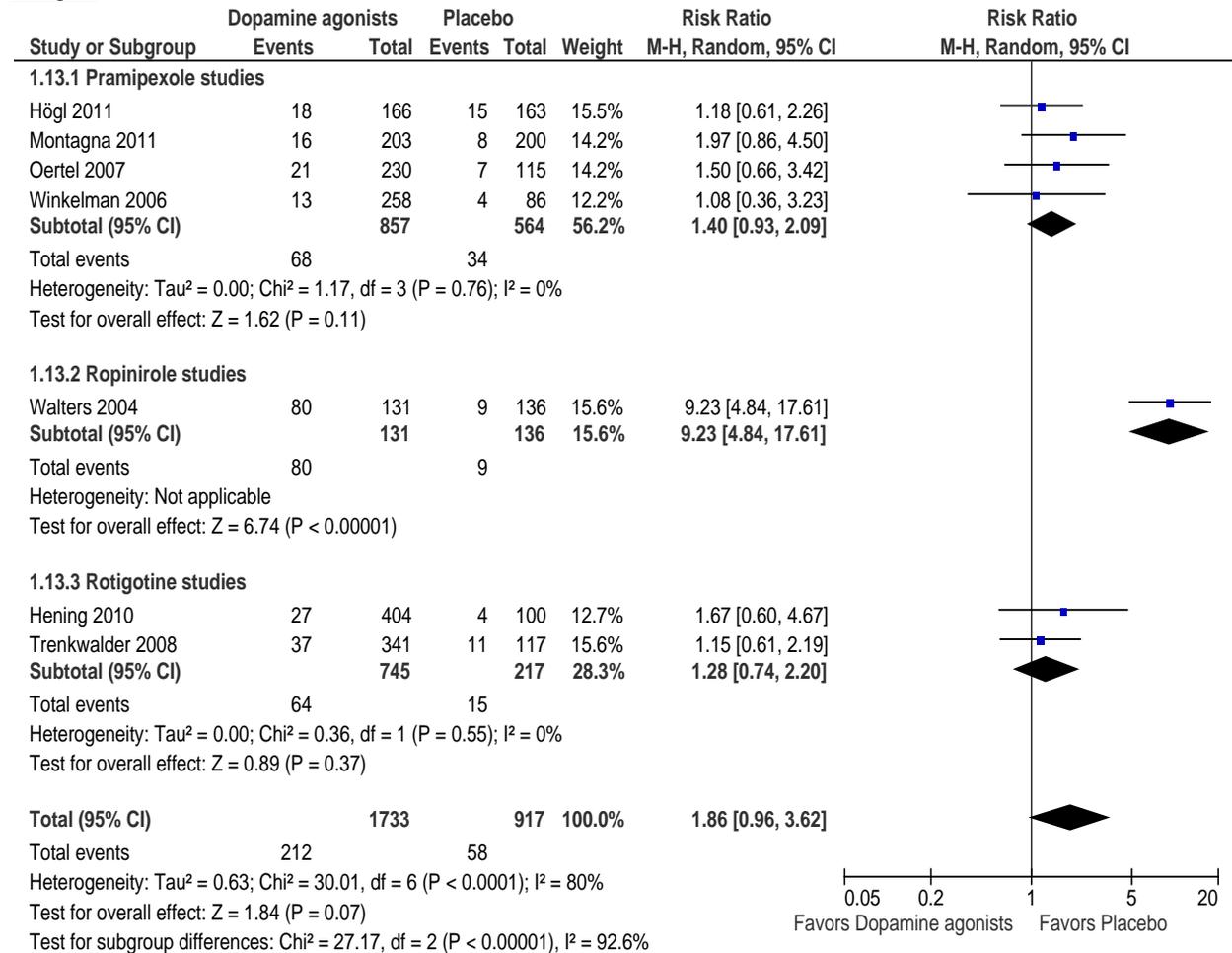
## Application site reactions (Rotigotine transdermal patch)



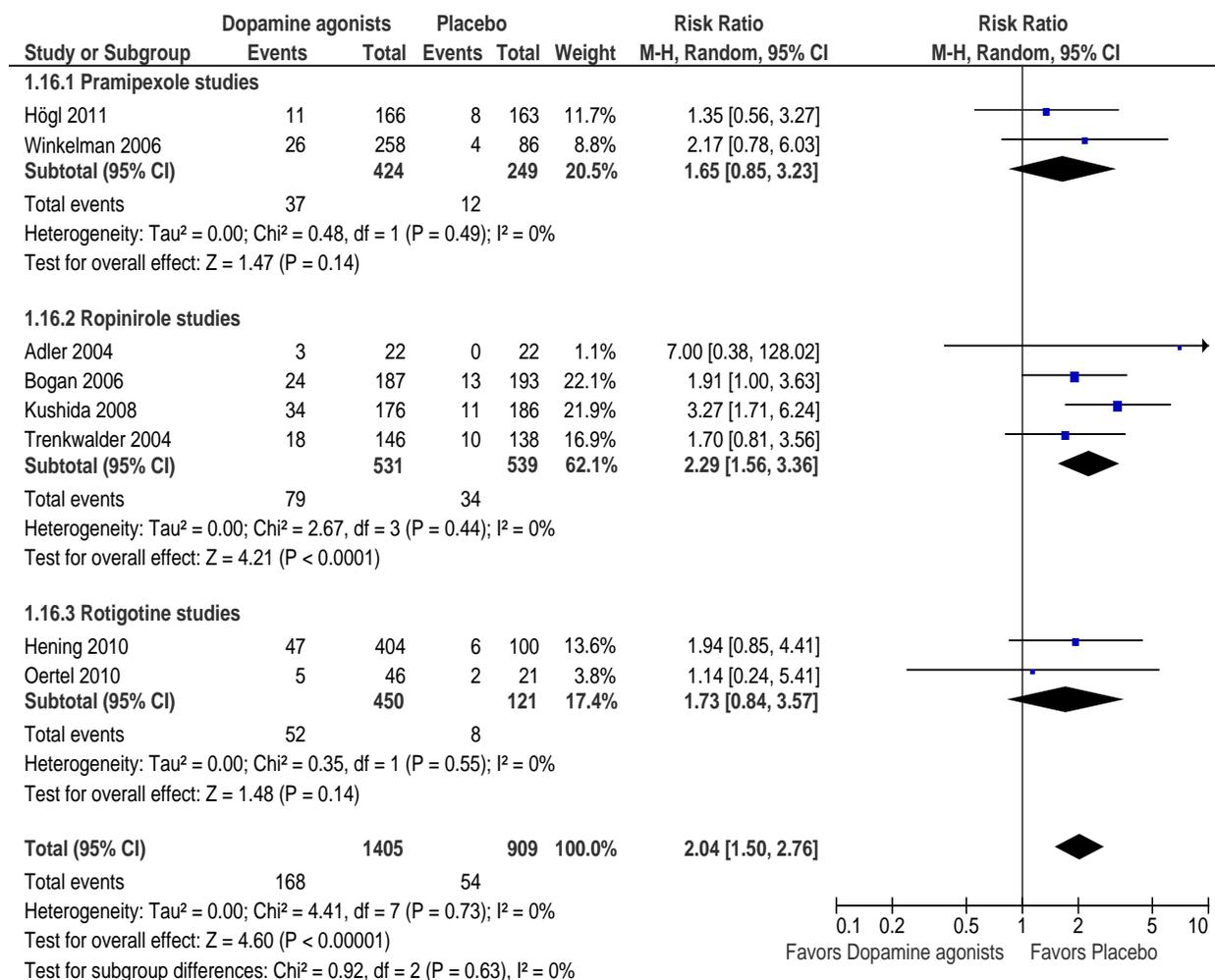
## Vomiting



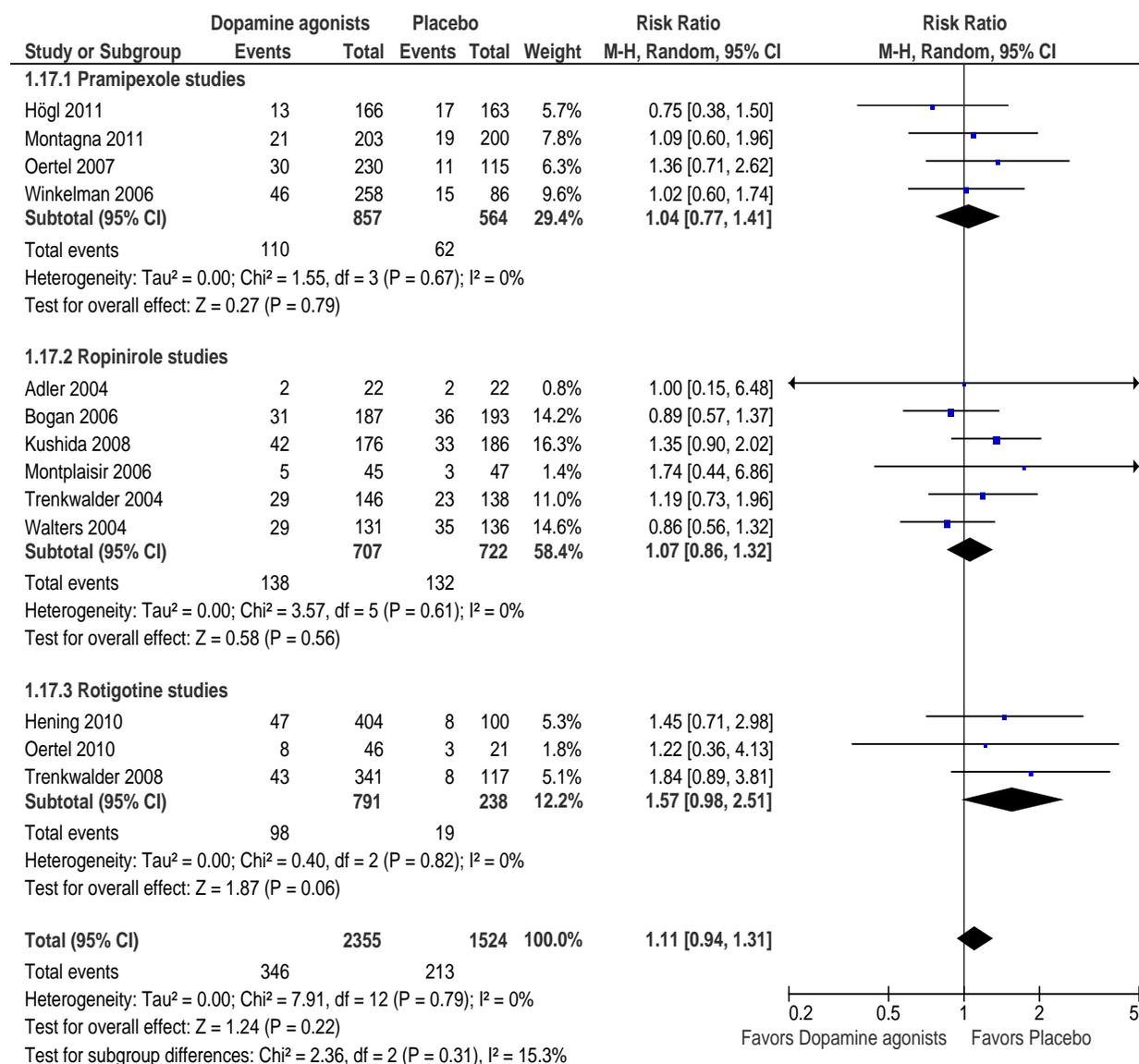
## Fatigue



## Somnolence



## Headache



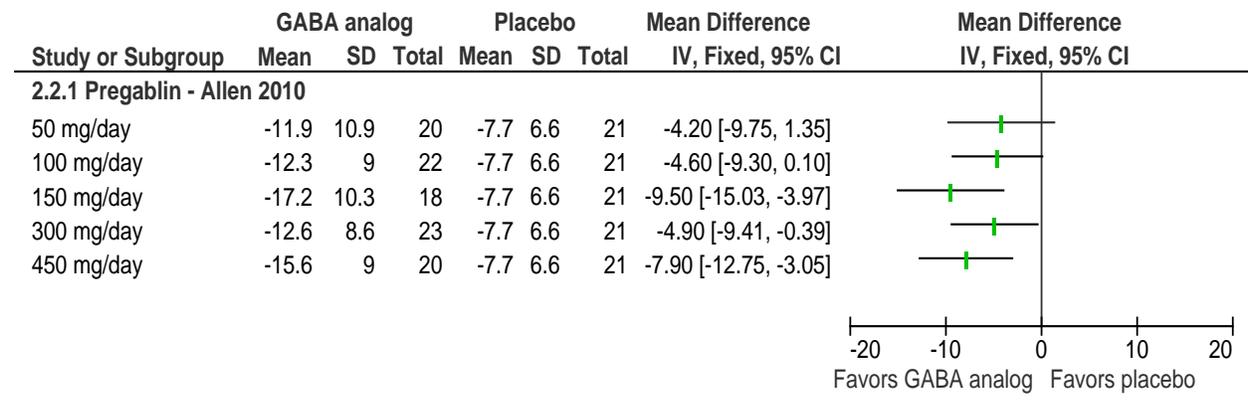
**Appendix. D. Figure3. Efficacy and Harms data for double-blind GABA analog trials**

IRLS Responders (≥50% score reduction) - fixed-dose study analyses

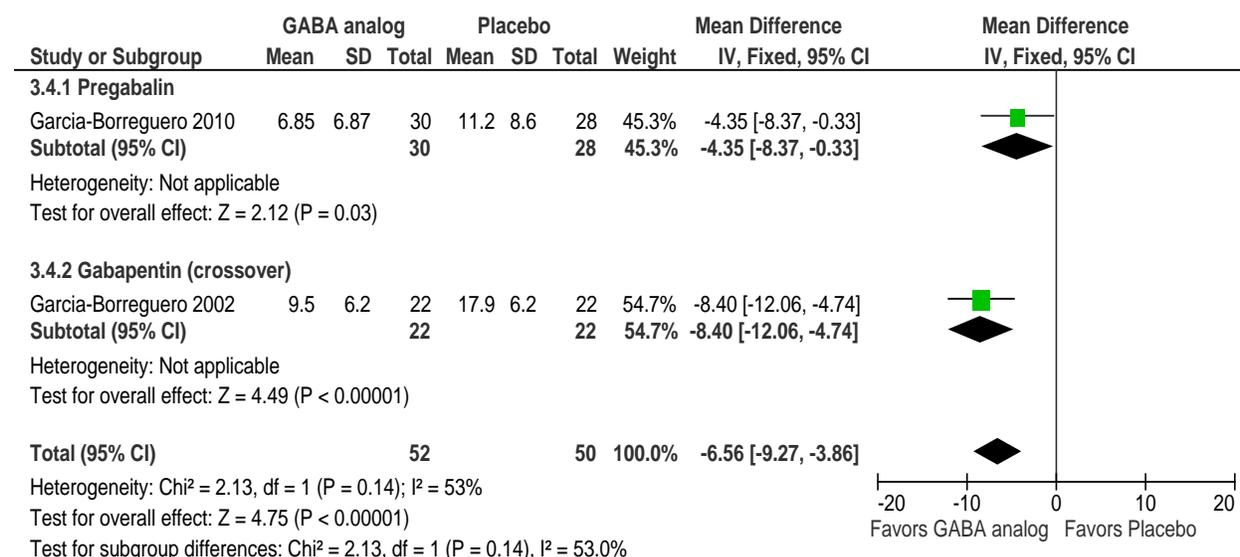
GABA analog      Placebo      Risk Ratio      Risk Ratio

]

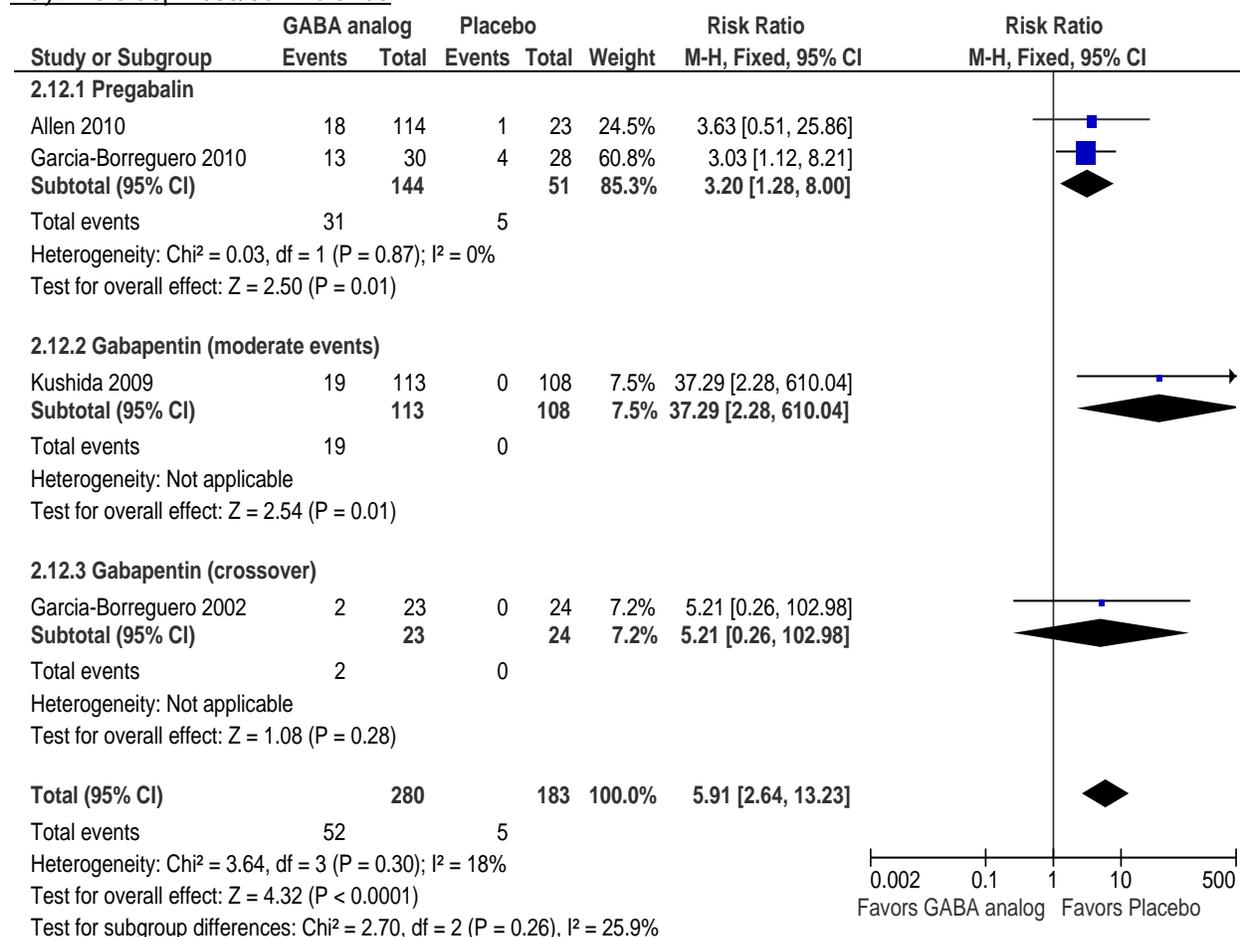
IRLS total score: Mean change from baseline - fixed-dose study analyses



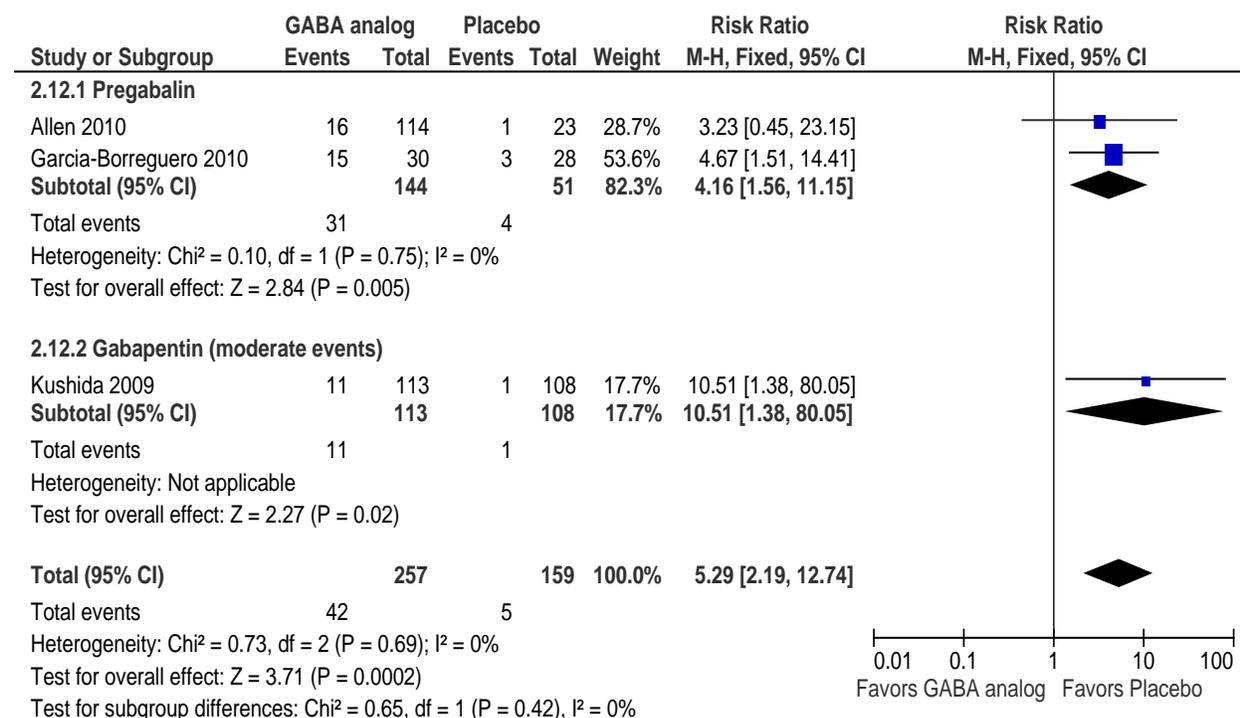
IRLS total score: mean score at end of treatment



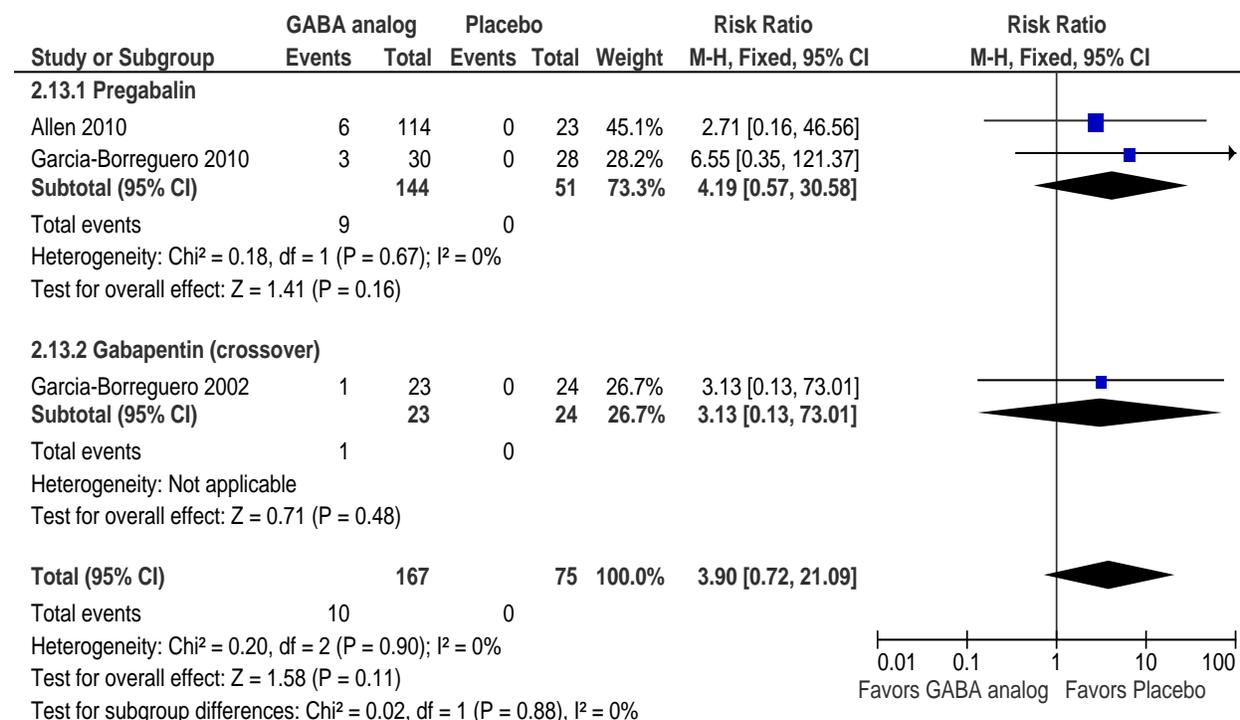
Daytime sleepiness/somnolence



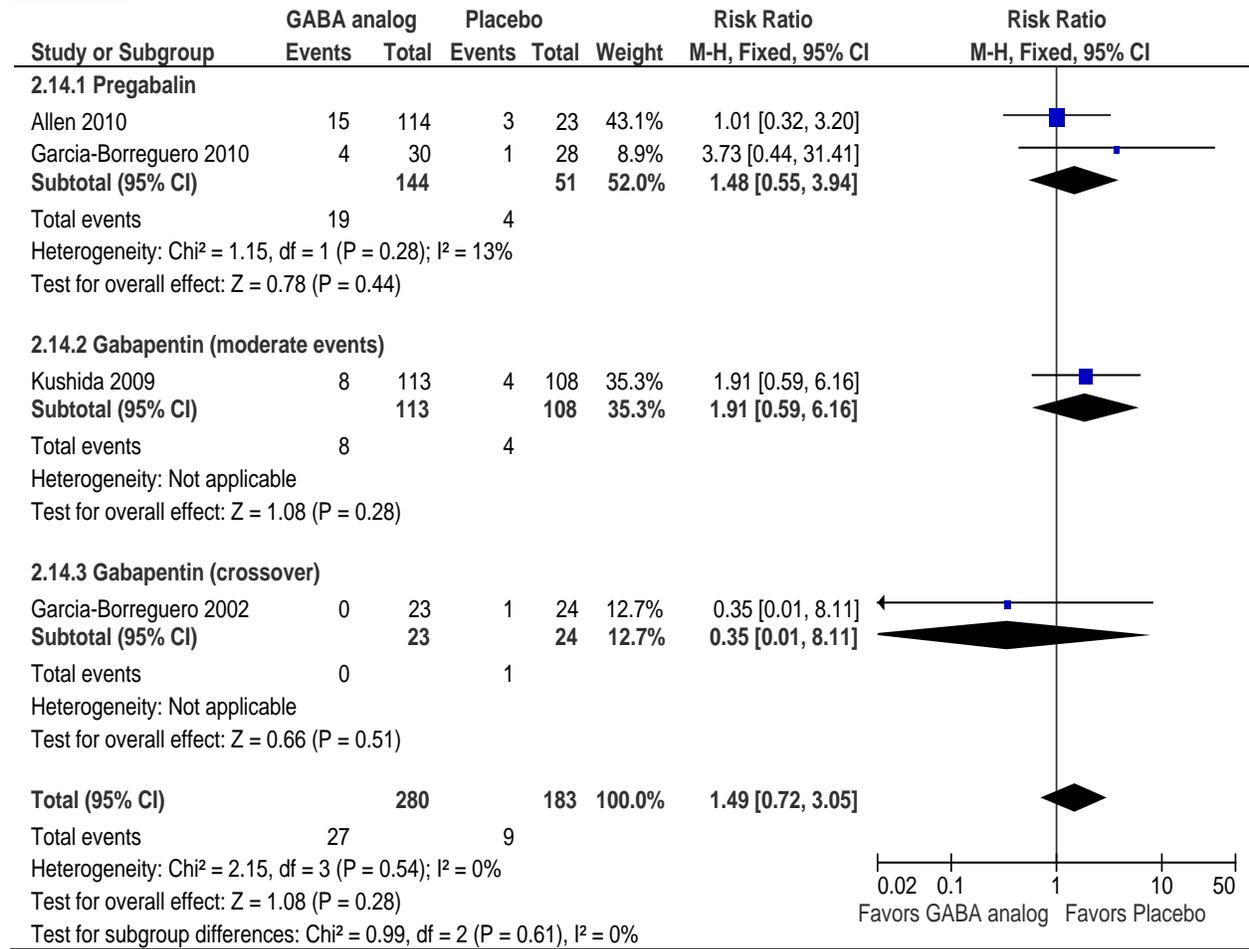
## Unsteadiness/dizziness



## Dry mouth

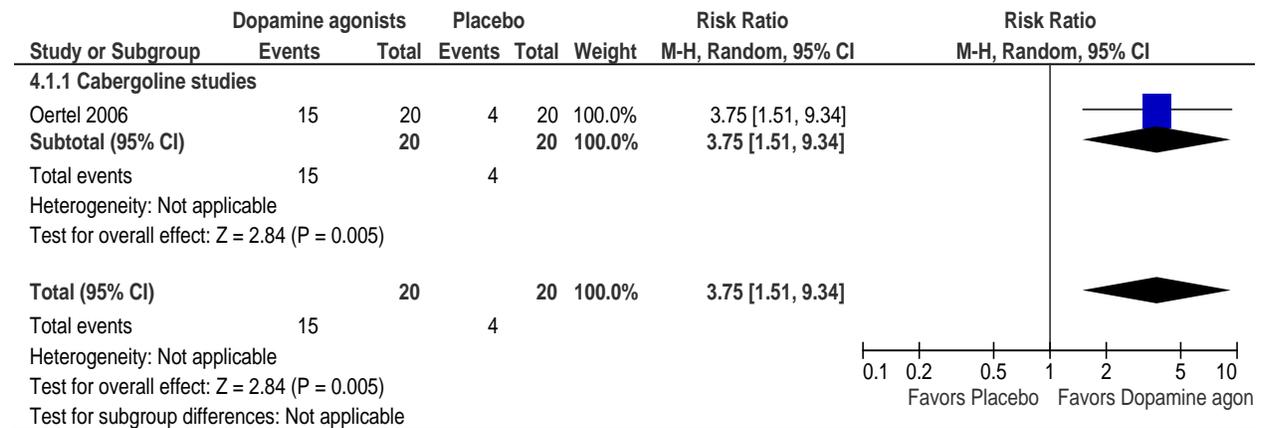


## Headache

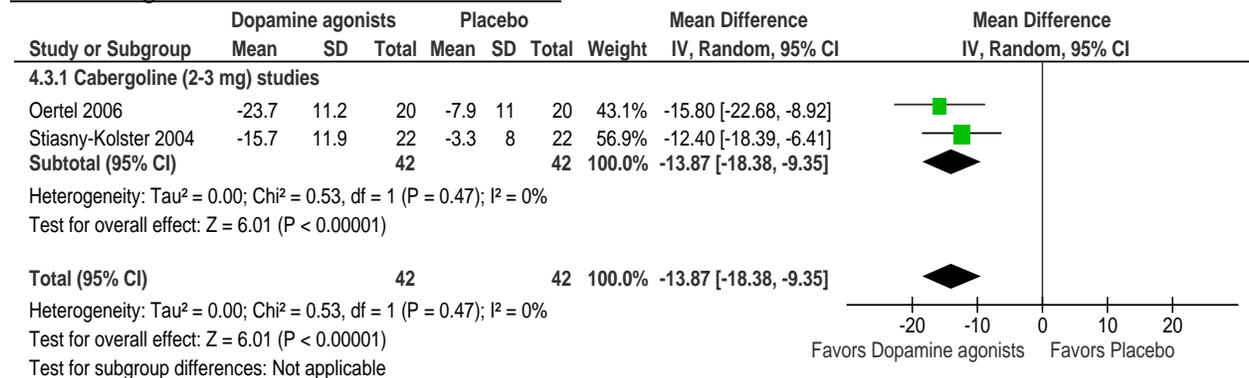


## Appendix D. Figure 4. Efficacy and Harms data for double-blind Cabergoline trials

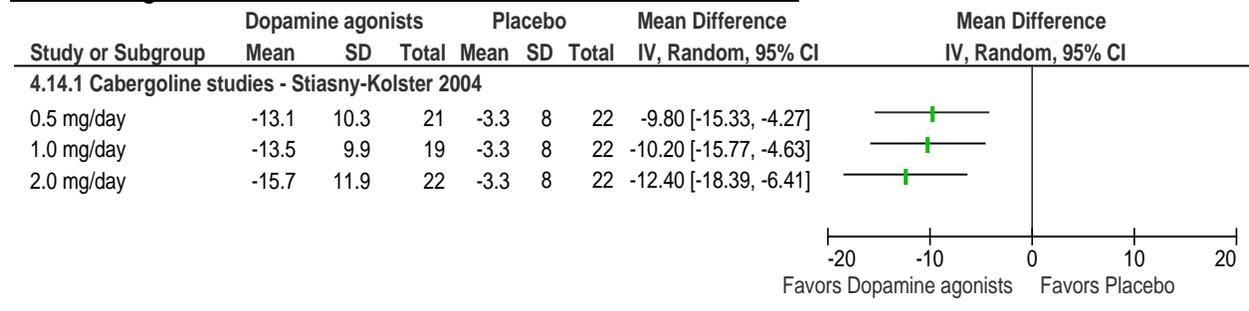
### International Restless Legs Scale (IRLS) Responders ( $\geq 50\%$ score reduction)



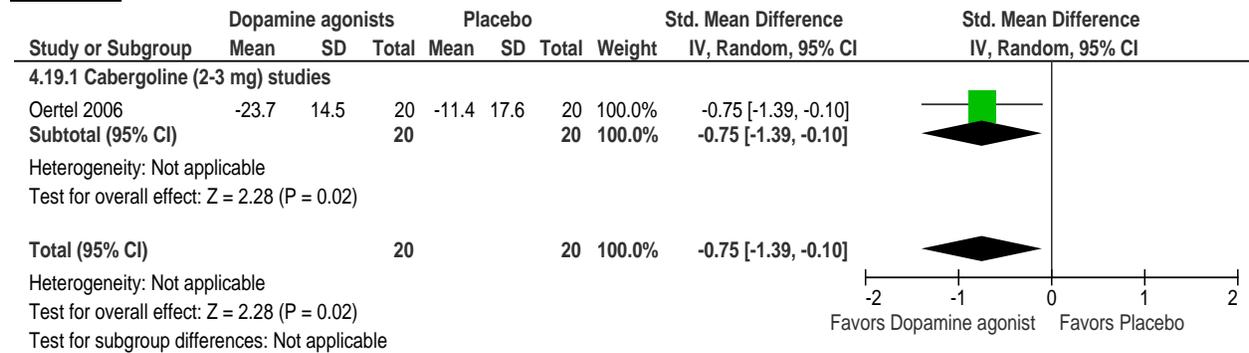
### Mean change in IRLS total score from baseline



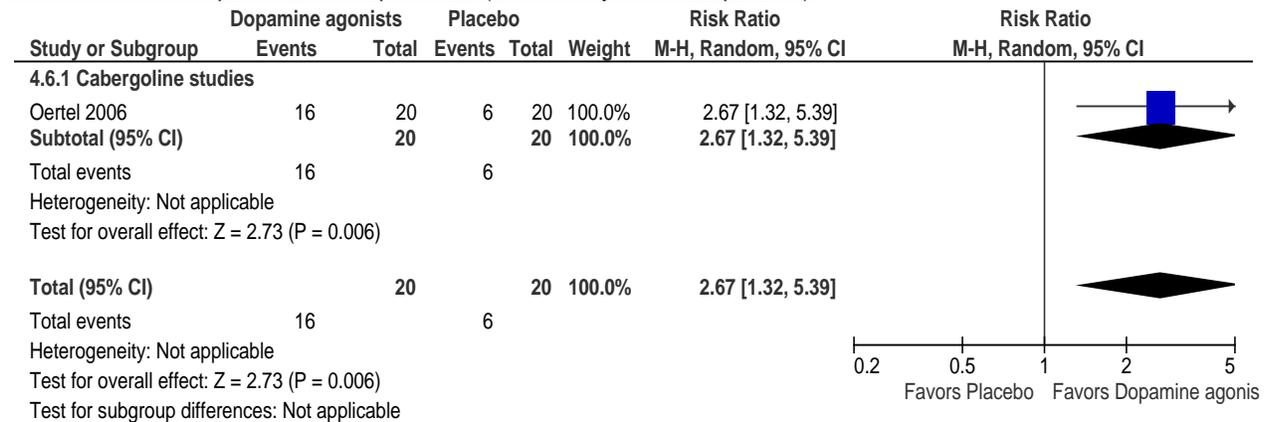
### Mean change in IRLS total score from baseline: Fixed-dose studies



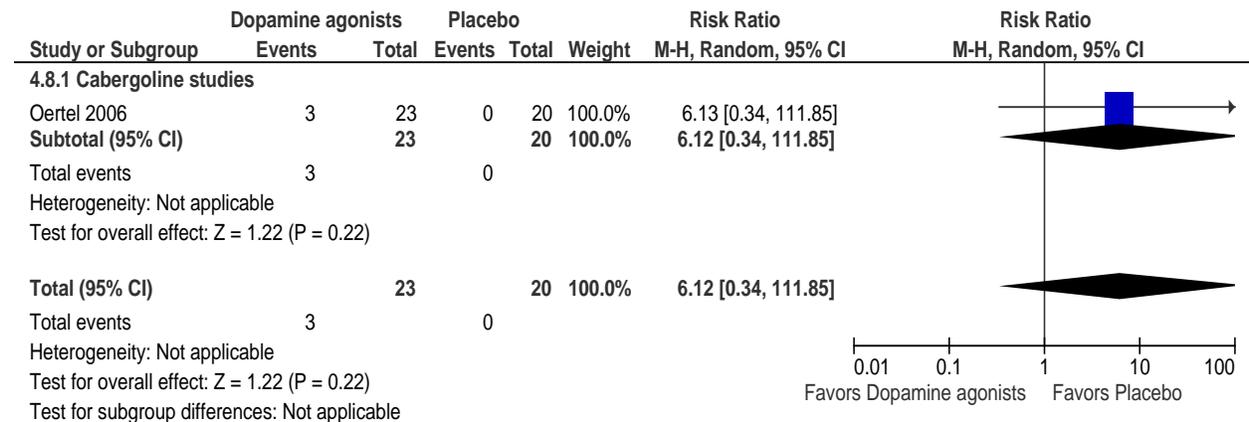
## RSL-QoL



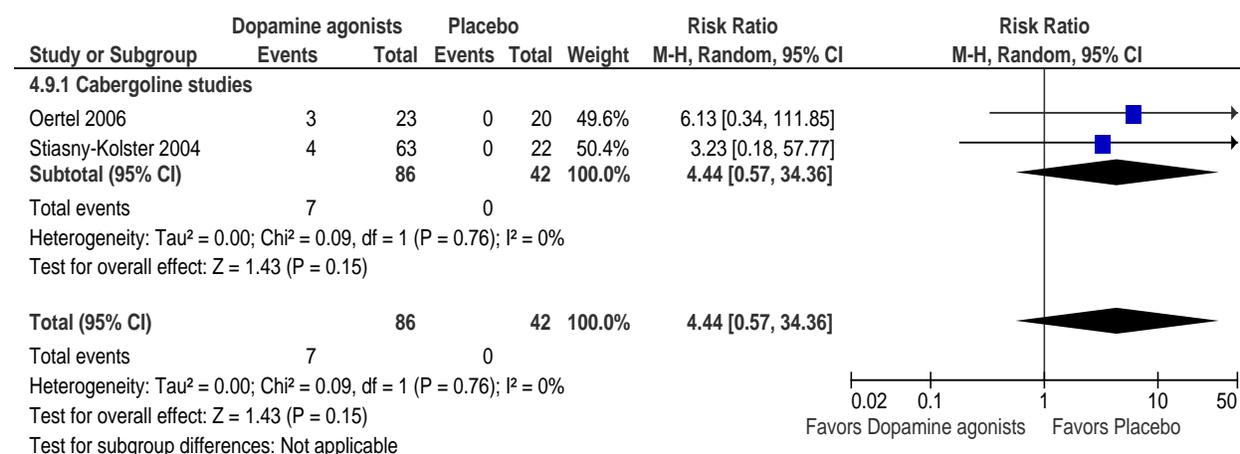
## Clinical Global Impression: Responders (much-very much improved)



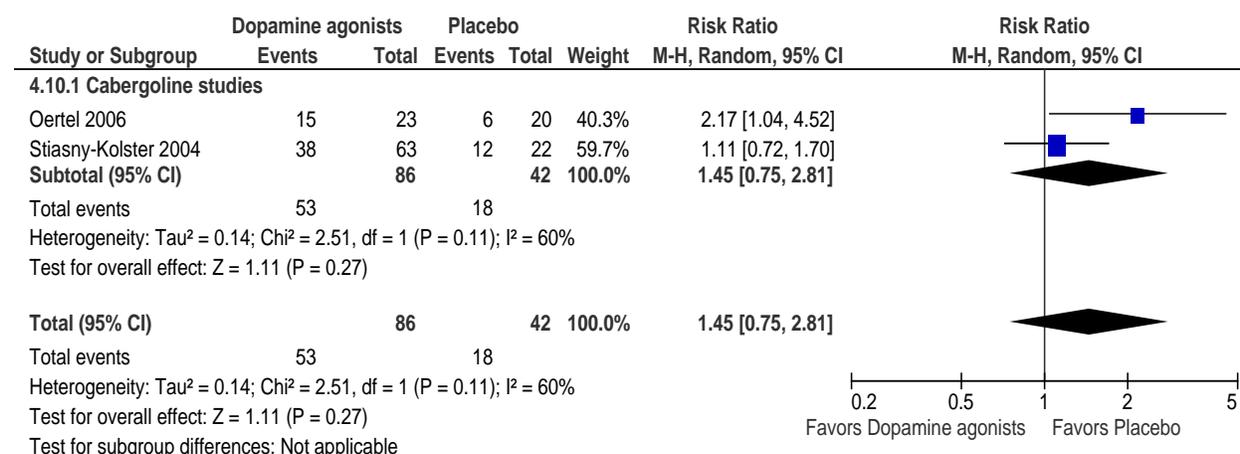
## Any study withdrawal



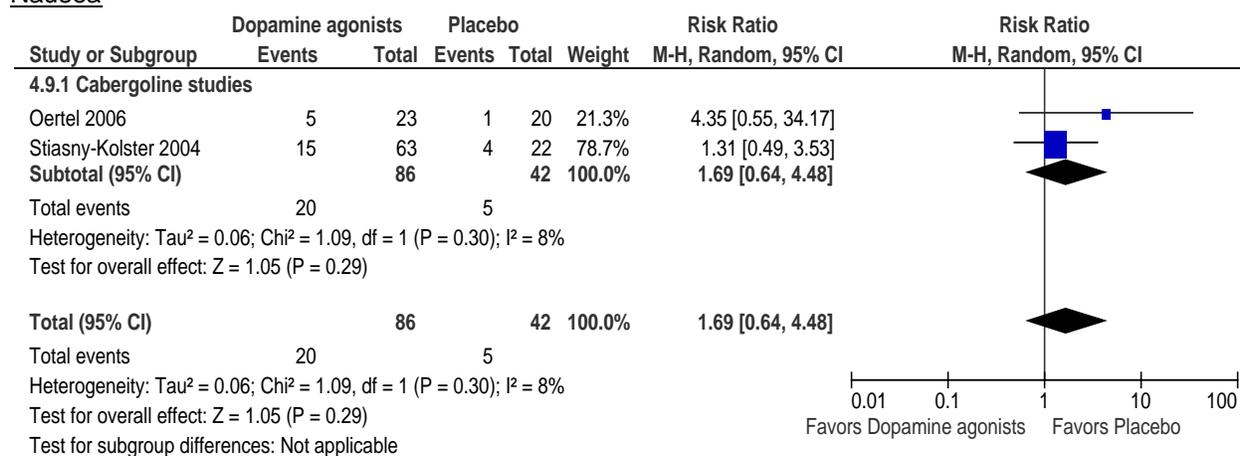
## Study withdrawals due to adverse effects



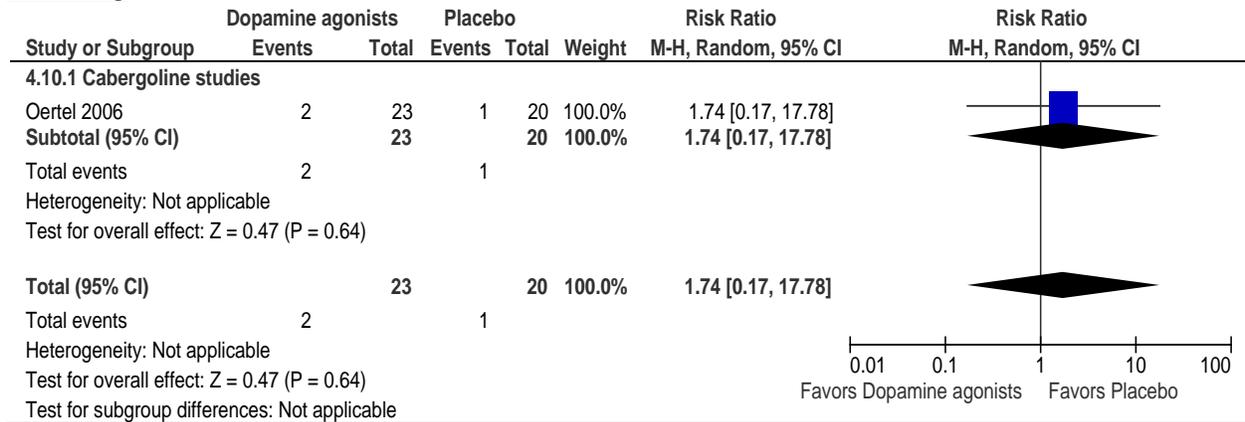
## Patients with ≥1 adverse event



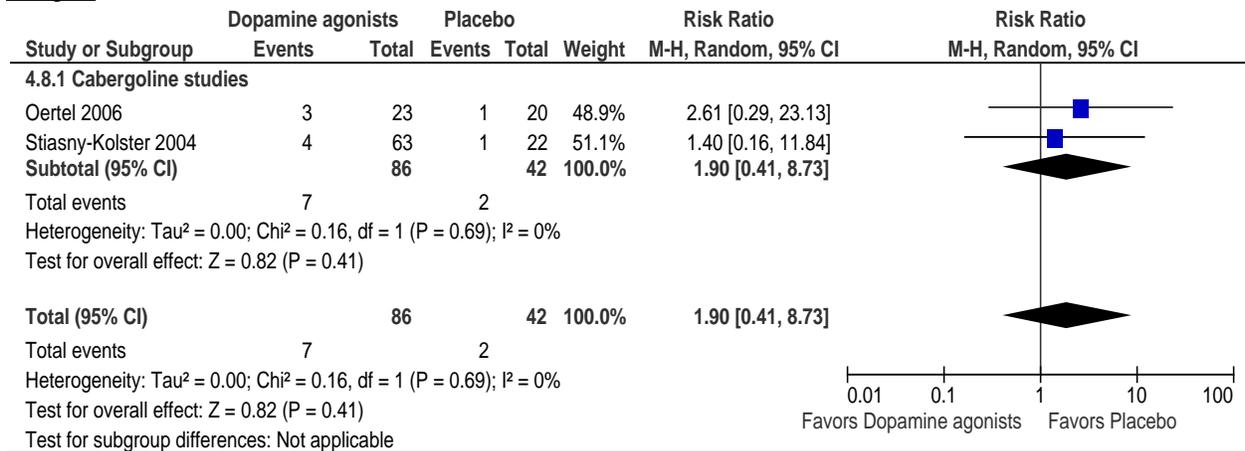
## Nausea



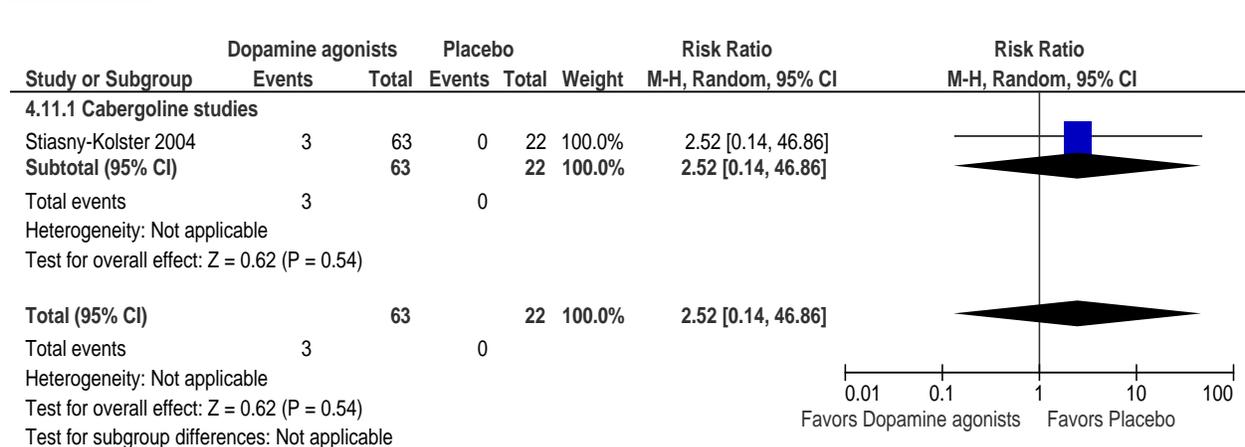
## Vomiting



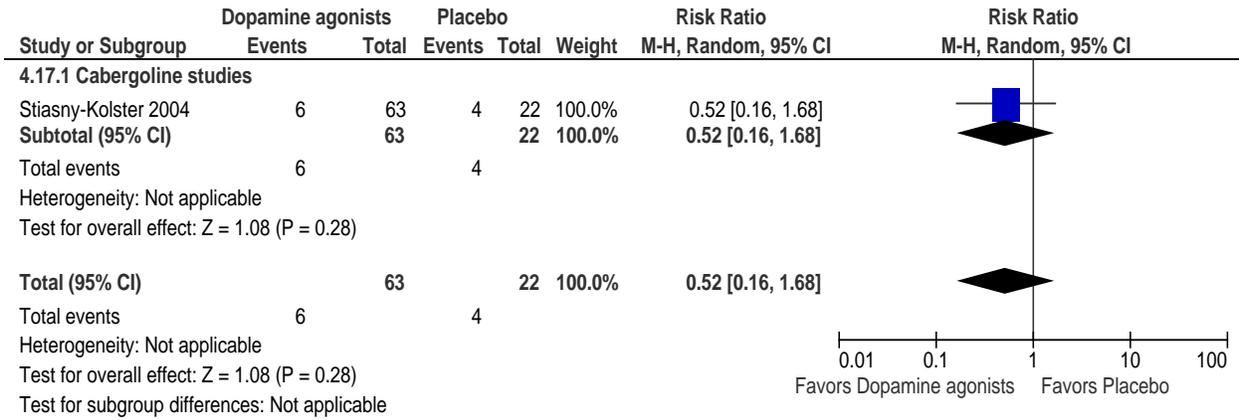
## Fatigue



## Somnolence

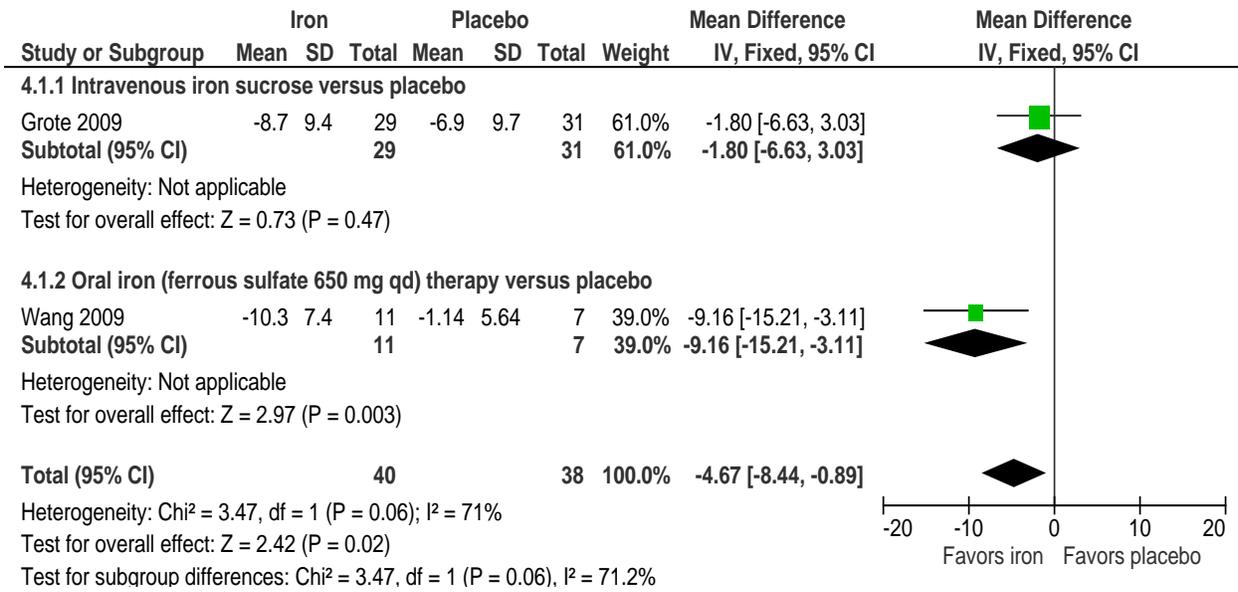


## Headache



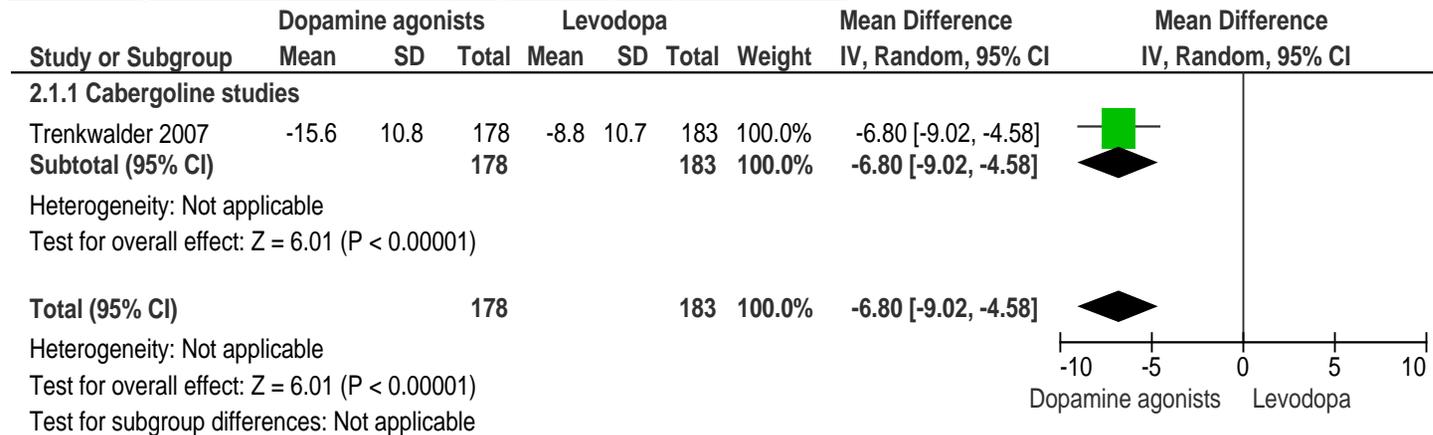
**Appendix D. Figure 5. Efficacy and Harms data for double-blind Iron therapy trials**

IRLS total score: Mean change from baseline

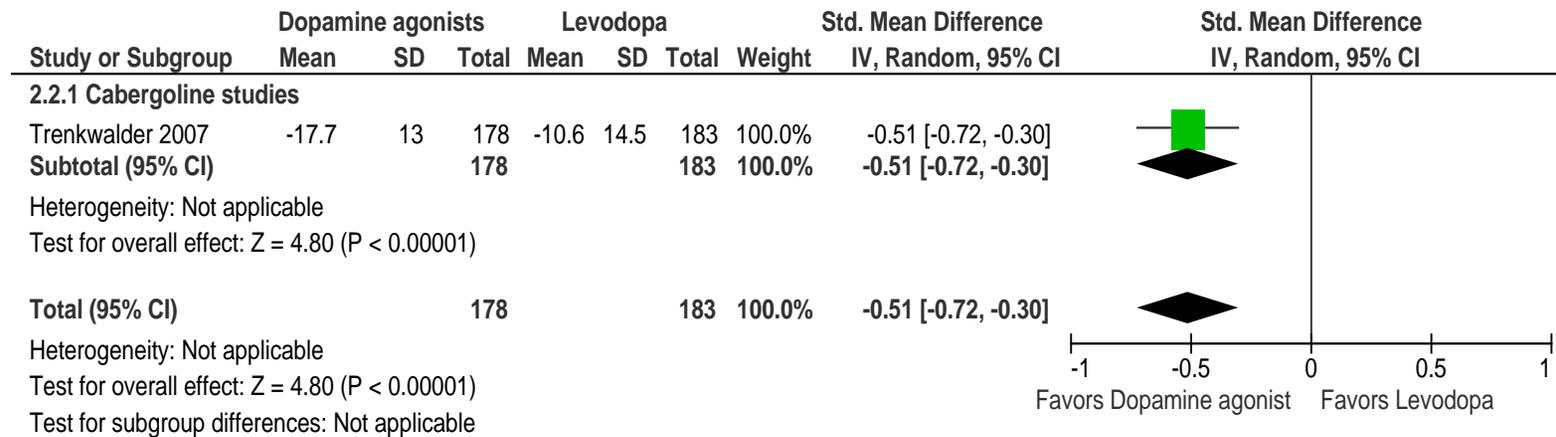


**Appendix D. Figure 6. Efficacy and Harms data for double-blind Cabergoline (dopamine agonists) vs. levodopa**

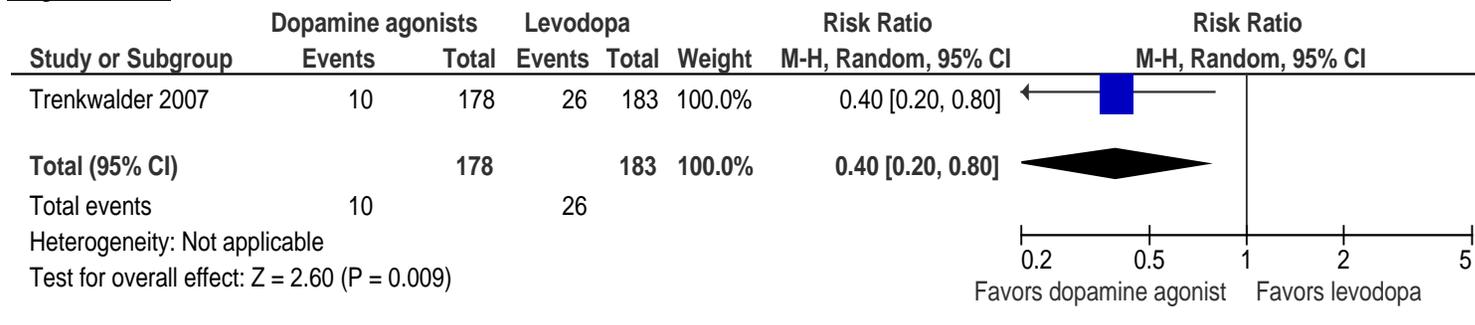
Mean change in International Restless Legs Scale (IRLS) from baseline



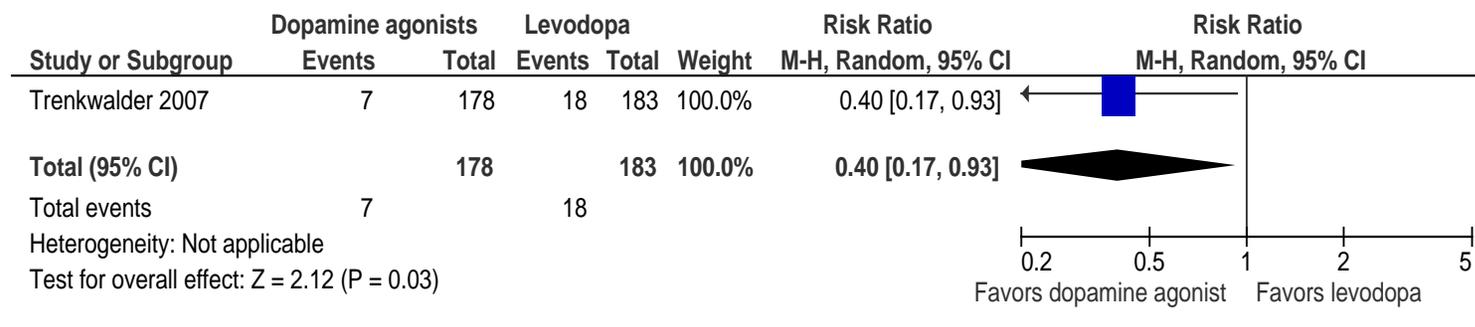
RSL-QoL



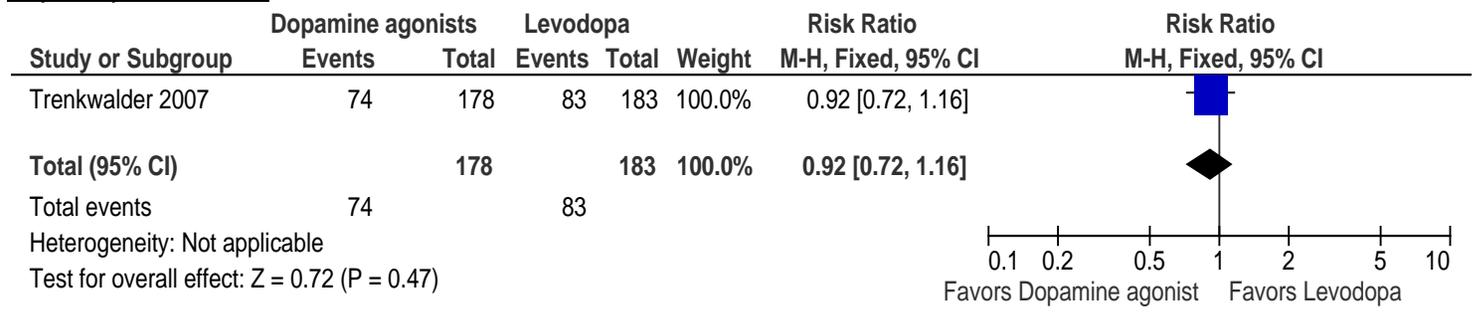
Augmentation



Augmentation leading to study withdrawal



Any study withdrawals

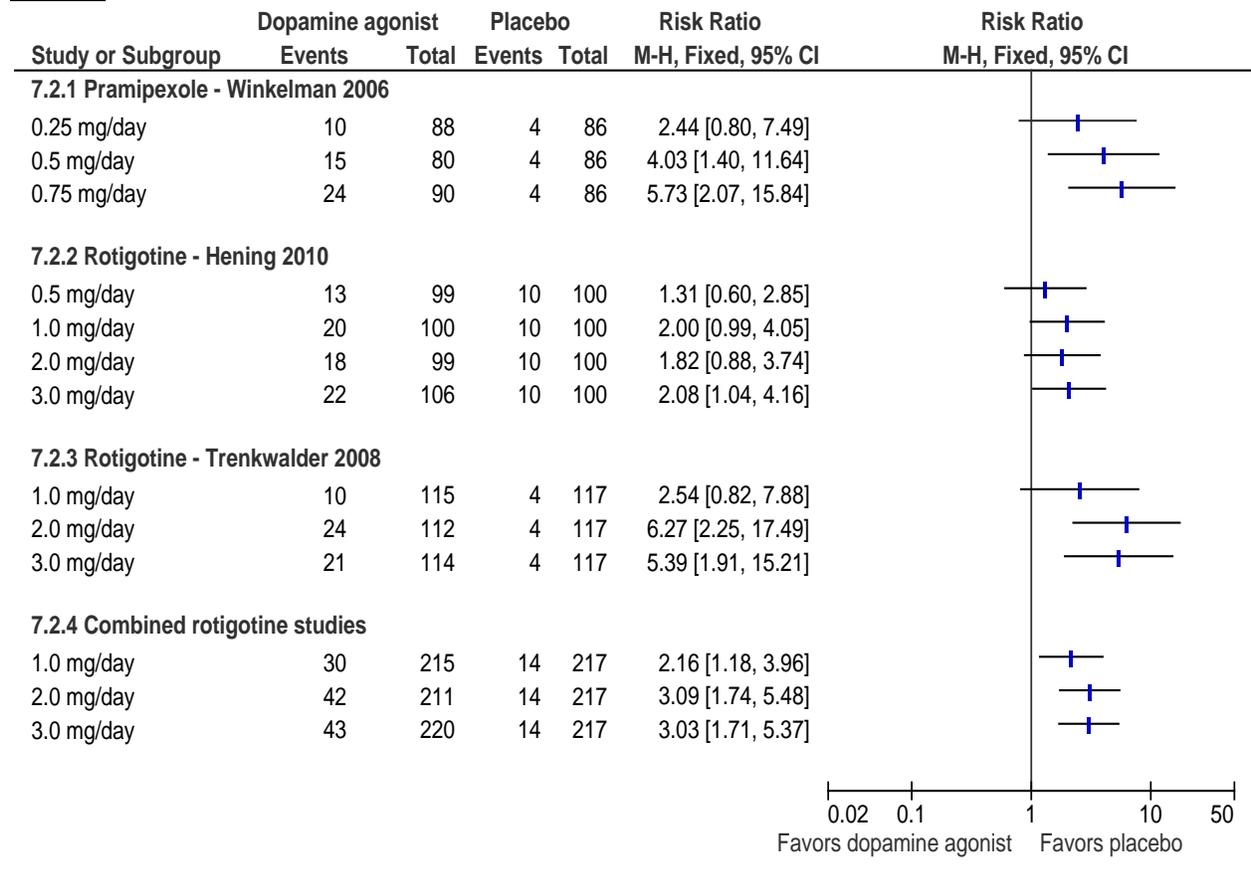


**Appendix D. Figure 7. Fixed-dose analyses of harms: Dopamine agonists**

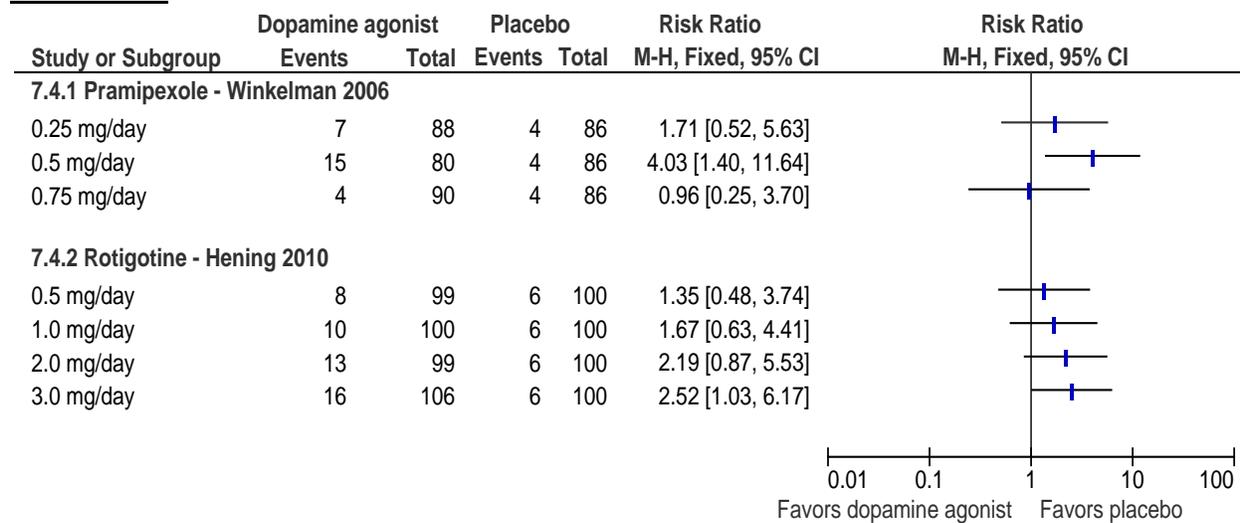
Application site reactions (rotigotine only)

Dopamine agonist      Placebo      Risk Ratio      Risk Ratio

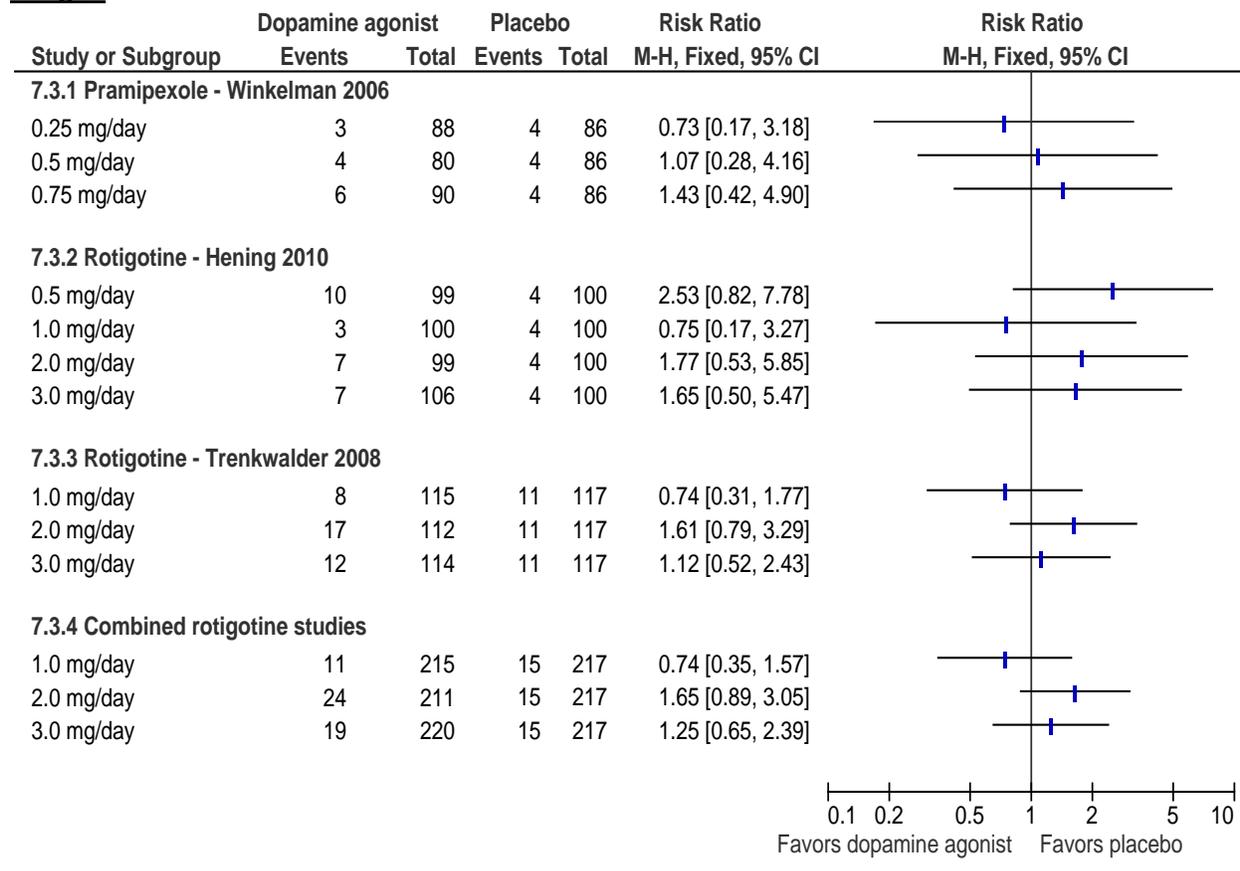
**Nausea**



## Somnolence



## Fatigue



**Appendix D. Table 8a. Self-rated quality of sleep for dopamine agonist trials: Medical Outcomes Scale- Sleep Problems Index II**

Study/ Duration (wks)	Treatment/ control	Baseline Score ( $\pm$ SD)*	Mean change from baseline ( $\pm$ SD)*	SMD [95%CI] between placebo
Hening, 2010 <sup>26</sup> (26)	Rotigotine (2 mg ** n=95)	NR	-21.5 (20.0)	0.35 [0.07 to 0.57]
	Placebo (n=99)	NR	-14.8 (18.1)	
Oertel, 2010 <sup>27</sup> (7)	Rotigotine (n=46)	53.3 (19.9)	-20.5 (21.4)	0.30 [-0.22 to 0.82]
	Placebo (n=21)	49.5 (20.8)	-14.1 (21.0)	
Trenkwalder, 2008 <sup>6</sup> (29)	Rotigotine (2 mg ** n=99)	NR	-20.1 (20.5)	0.54 [0.25 to 0.82]
	Placebo (n=99)	NR	-10.0 (16.7)	
Ferini-Strambi, 2008 <sup>†4</sup> (12)	Pramipexole(n=178)	NR	-19.5 (19.2)	0.36 [0.15 to 0.57]
	Placebo (n=178)	NR	-12.9 (17.8)	
Kushida, 2008 <sup>†3</sup> (12)	Ropinirole (n=174)	NR	-22.4 (23.5)	0.24 [0.04 to 0.45]
	Placebo (n=183)	NR	-16.8 (22.4)	
Bogan, 2006 <sup>9</sup> (12)	Ropinirole (n=176)	52.0 (16.6)	-22.8 (18.0)	0.45 [0.24 to 0.66]
	Placebo (n=182)	50.4 (15.6)	-14.6 (18.0)	
Trenkwalder, 2004 <sup>†12</sup> (12)	Ropinirole (n=140)	NR	-14.8 (22.0)	0.29 [0.05 to 0.53]
	Placebo (n=130)	NR	-9.0 (18.2)	
Walters, 2004 <sup>†13</sup> (12)	Ropinirole (n=123)	NR	-16.5 (20.0)	0.50 [0.25 to 0.75]
	Placebo (n=129)	NR	-7.0 (18.1)	

SD = standard deviation; SMD = standardized mean difference

\* If provided.

\*\* Fixed-dose study (range 0.5-3mg), 2 mg dose used for analysis.

† Data not reported in publication but was obtained from a prior systematic review (Scholz H, Trenkwalder C, Kohnen R, Kriston L, Riemann D, Hornyak M. Dopamine agonists for the treatment of restless legs syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD006009. DOI: 10.1002/14651858.CD006009.pub2).

**Table 8b. Self-rated quality of daytime sleepiness for dopamine agonist trials: Epworth Sleepiness Scale**

Study/ Duration (wks)	Treatment/ control	Baseline Score ( $\pm$ SD)*	Mean change from baseline ( $\pm$ SD)*	SMD [95%CI] between placebo
Winkelman, 2006 <sup>11</sup> (12)	Pramipexole(n=253)	7.5 (4.5)	-1.8 (0.2)	P=0.30**
	Placebo (n=85)	8.1 (4.4)	-1.4 (0.4)	
Adler, 2004 <sup>8</sup> (4 x 2) <sup>†</sup>	Ropinirole (n=22)	NR	6.9 (7.2) <sup>††</sup>	-1.2 [-3.7 to 1.2] <sup>‡</sup>
	Placebo (n=22)	NR	8.1 (6.3) <sup>††</sup>	

SD = standard deviation; SMD = standardized mean difference

\* If provided.

\*\* SMD not calculated, unclear if mean reduction represents all fixed doses of pramipexole combined.

† Crossover trial, two 4 week treatment periods

†† Scores at end of treatment

‡ Mean difference

**Appendix D. Table 9a. Self-rated quality of sleep for GABA analog trials: Medical Outcomes Scale-Sleep Problems Index II or Pittsburgh Sleep Quality Index**

Study/ Duration (wks)	Treatment/ control	Instrument	Baseline Score (±SD)*	Mean change from baseline (±SD)*	SMD [95%CI] or P-value between placebo
Allen, 2011 <sup>29</sup> (6)	Pregabalin (300 mg ** n=24)	MOS-SPI-II, 9-item	NR	-22.3 (19.1)	-0.29 [-0.29 to 0.86]
	Placebo (n=23)		NR	-16.8 (18.2)	
Garcia-Borreguero, 2010 <sup>15</sup> (12)	Pregabalin (n=30)	MOS-sleep adequacy	NR	NR	NR, P=0.001
	Placebo (n=23)		NR	NR	
Kushida, 2009 <sup>16</sup> (12)	Gabapentin (XP13515)(n=112)	MOS-sleep adequacy	NR	27.7 (29.9)	0.50 [0.23 to 0.76]
	Placebo (n=108)		NR	13.4 (27.4)	
	Gabapentin (XP13515)(n=112)	PSQI	NR	NR	NR, "all PSQ outcomes significantly improved with XP13515 at week 12"
	Placebo (n=108)		NR	NR	
Garcia-Borreguero, 2002 <sup>17</sup> (6 x 2) †	Gabapentin (n=22)	PSQI	9.7 (all patients)	6.4 (1.9) ††	P<0.001
	Placebo (n=22)			9.4 (1.9) ††	

Medical Outcomes Scale- Sleep Problems Index II; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; SMD = standardized mean difference

\* If provided.

\*\* Fixed dose study (range 50-400 mg), 300 mg dose used for analysis.

† Crossover trial, two 6 week treatment periods

†† Scores at end of treatment

**Appendix D. Table 9b. Self-rated quality of daytime sleepiness for dopamine agonist trials: Epworth Sleepiness**

Study/ Duration (wks)	Treatment/ control	Baseline Score (±SD)*	Mean change from baseline (±SD)*	SMD [95%CI] between placebo
Kushida, 2009 <sup>16</sup> (12)	Gabapentin (XP13515)(n=112)	9.8 (4.9)	6.1 (4.1) **	-0.21 [-0.47 to 0.06]
	Placebo (n=108)	9.2 (4.5)	7.0 (4.6) **	

SD = standard deviation; SMD = standardized mean difference

\* If provided.

\*\* Scores at end of treatment

**Appendix D. Table 10. Self-rated quality of sleep for the non-pharmacologic trials**

<b>Study/ Duration (wks)</b>	<b>Treatment/ control</b>	<b>Instrument</b>	<b>Baseline Score (<math>\pm</math>SD)*</b>	<b>Mean change from baseline (<math>\pm</math>SD)*</b>	<b>P-value between placebo</b>
Cuellar, 2009 <sup>23</sup> (8)	Valerian (n = 17)	PSQ	14.4 (3.7)	4.5 (5.3)	0.94
	Placebo (n = 20)		12.4 (5.0)	4.4 (4.8)	
Cuellar, 2009 <sup>23</sup> (8)	Valerian (n = 17)	ESS	11.7 (5.4)	3.4 (4.4)	0.64
	Placebo (n = 20)		10.4 (6.1)	2.8 (3.7)	
Lettieri, 2009 <sup>24</sup> (4)	Compression device (n = 21)	ESS	11.2 (4.4)	6.5 (4.0)	0.04
	Sham device (n = 14)		11.3 (3.9)	10.6 (3.8)	

ESS = Epworth Sleepiness Scale; PSQ = Pittsburgh Sleep Quality Index; SD = standard deviation.

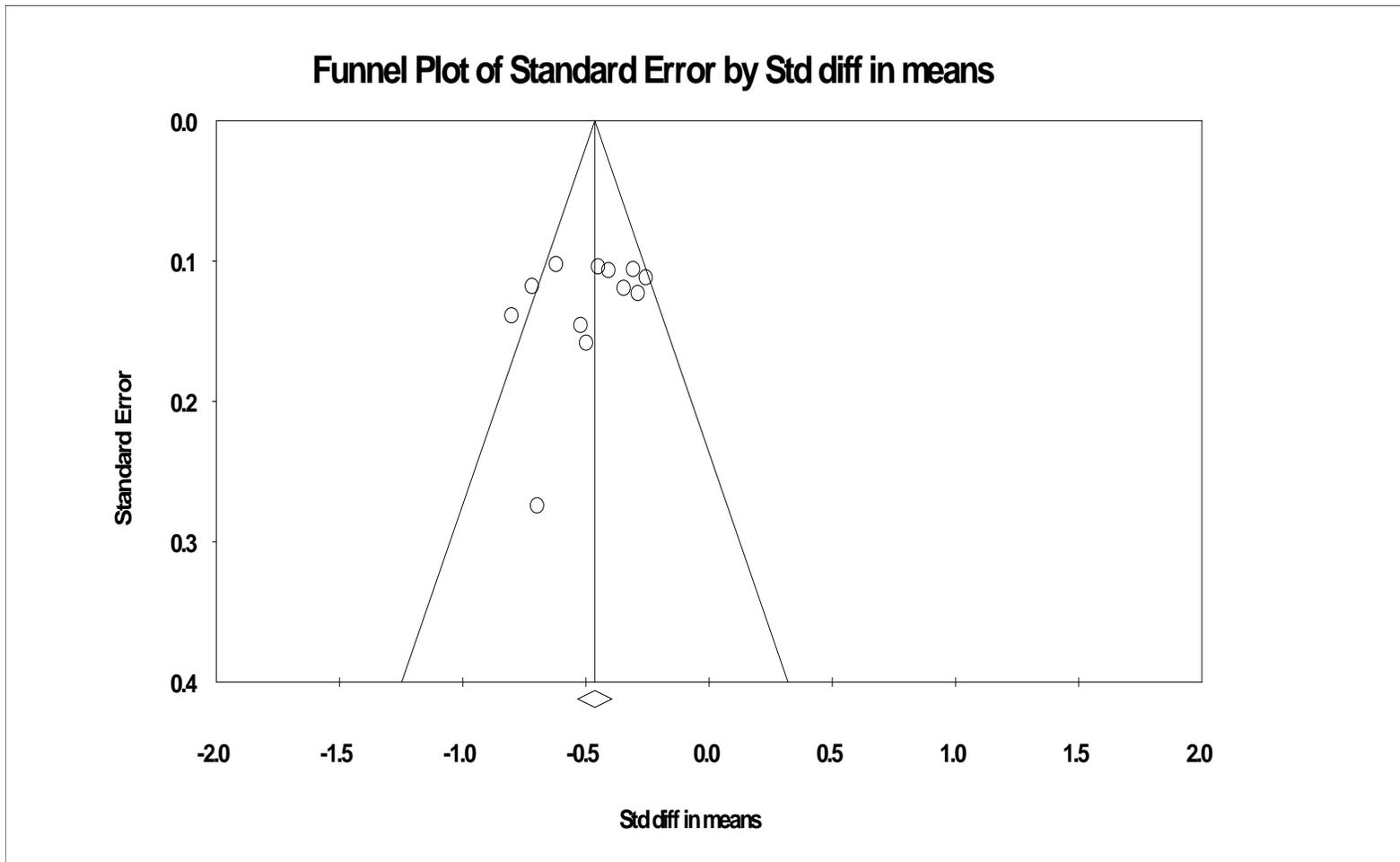
**Appendix D. Table 11. Self-rated quality of life and of sleep for iron trials**

<b>Study/ Duration (wks)</b>	<b>Treatment/ control</b>	<b>Instrument</b>	<b>Baseline Score</b>	<b>Mean change from baseline</b>	<b>P-value between placebo</b>
Grote, 2009 <sup>21</sup>  (52)	Intravenous iron 200 mg x 5 occasions (1000 mg) (n=29)	ESS	Median 9.0 (2-18)	NR	NR "no statistical difference between treatment groups at any point of the study"
	Placebo (n=31)		Median 9.5 (1-18)	NR	
Wang, 2009 <sup>22</sup> (12)	Oral iron 650 mg daily (n=11)	Overall Quality of life		Improved 7 (64%)	P=0.07
	Placebo (n=7)			Improved 1 (14%)	

ESS = Epworth Sleepiness Scale. SD = standard deviation

\* Proportion of participants reporting "Improved" versus "stayed the same or worsened."

Appendix D. Figure 8. Funnel plot for Mean change in IRLS total score from baseline



**Appendix D. Table 12. Patient global impressions responders (PGI) at end of treatment for dopamine agonist studies**

<b>Study, year</b>	<b>Duration (weeks)</b>	<b>Drug and daily dosage / control</b>	<b>Positive response % (n/N)</b>	<b>Risk ratio [95% CI]</b>
Högl, 2011 <sup>1</sup>	26	Pramipexole 0.125-0.75 mg	62.3 (101/162)	1.42 [1.15 to 1.75]
		Placebo	44.0 (70/159)	
Montagna, 2011 <sup>2</sup>	12	Pramipexole 0.125-0.75 mg	62.9 (112/178)	1.66 [1.33 to 2.06]
		Placebo	38.0 (68/179)	
Ferini-Strambi, 2008 <sup>4</sup>	12	Pramipexole 0.125-0.75 mg	62.9 (112/178)	1.66 [1.33 to 2.06]
		Placebo	38.0 (68/179)	
Oertel, 2007 <sup>7</sup>	6	Pramipexole 0.125-0.75 mg	61.6 (138/224)	1.95 [1.46 to 2.61]
		Placebo	31.6 (36/114)	
Winkelman, 2006 <sup>11</sup>	12	Pramipexole 0.125-0.75 mg	42.5 (108/224)	3.01 [1.75 to 5.19]
		Placebo	14.1 (12/85)	
Kushida, 2008 <sup>5</sup>	12	Ropinirole 1-12 mg	78.2 (136/174)	1.52 [1.29 to 1.79]
		Placebo	51.4 (94/183)	

CI = confidence intervals

**Appendix D. Table 13. Clinical global impressions (CGI) responders (much-very much improved) at end of treatment for the dopamine agonist studies**

Study, year	Duration (weeks)	Drug and daily dosage / control	Positive response % (n/N)	Risk ratio [95% CI]
Ferini-Strambi, 2008 <sup>4</sup>	12	Pramipexole 0.125-0.75 mg	66.3 (118/178)	1.65 [1.34 to 2.03]
		Placebo	40.2 (72/179)	
Högl, 2011 <sup>1</sup>	26	Pramipexole 0.125-0.75 mg	68.5 (111/162)	1.36 [1.13 to 1.64]
		Placebo	50.3 (80/159)	
Montagna, 2011 <sup>2</sup>	12	Pramipexole 0.125-0.75 mg	69.3 (140/202)	1.88 [1.53 to 2.30]
		Placebo	36.9 (72/195)	
Oertel, 2007 <sup>7</sup>	6	Pramipexole 0.125-0.75 mg	62.9 (141/224)	1.94 [1.46 to 2.57]
		Placebo	32.5 (37/114)	
Winkelman, 2006 <sup>11</sup>	12	Pramipexole 0.125-0.75 mg	72.0 (180/250)	1.41 [1.13 to 1.76]
		Placebo	51.2 (43/84)	
Bogan, 2006 <sup>9</sup>	12	Ropinirole 0.25-4 mg	73.3 (137/187)	1.30 [1.12 to 1.51]
		Placebo	56.5 (109/193)	
Hening, 2010 <sup>26</sup>	26	Rotigotine 0.5,1,2,3 mg	69.5 (264/380)	1.22 [1.01 to 1.46]
		Placebo	57.1 (56/98)	
Kushida, 2008 <sup>5</sup>	12	Ropinirole 1-12 mg	70.9 (124/175)	1.42 [1.19 to 1.68]
		Placebo	50.0 (92/184)	
Montplaisir, 2006 <sup>10</sup>	12	Ropinirole 2.05 mg (mean)	68.9 (31/45)	1.48 [1.02 to 2.13]
		Placebo	46.7 (21/45)	
Oertel, 2010 <sup>27</sup>	7	Rotigotine 1-3 mg	84.1 (37/44)	1.40 [0.96 to 2.05]
		Placebo	60.0 (12/20)	
Trenkwalder, 2004 <sup>12</sup>	12	Ropinirole 0.25-4 mg	53.4 (78/146)	1.31 [1.02 to 1.68]
		Placebo	40.9 (56/137)	
Trenkwalder, 2008 <sup>6</sup>	29	Rotigotine 1-3 mg	69.4 (213/307)	1.52 [1.22 to 1.91]
		Placebo	45.5 (46/101)	
Walters, 2004 <sup>13</sup>	12	Ropinirole 0.25-4 mg	59.5 (78/131)	1.51 [1.17 to 1.94]
		Placebo	39.6 (53/134)	

CI = confidence intervals

# **Appendix E**

**Appendix E. Table 1. Withdrawals and adverse effects for the dopamine agonist trials Part A**

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1 serious adverse effects n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
<b>Pramipexole</b>										
Ferini-Stamb, 2008 <sup>4</sup>	27/182 (14.8)	52/187 (27.8)	17/182 (9.3)	16/187 (8.6)	106/182 (58.2)	86/187 (46.0)	47/182 (25.8)	49/187 (26.2)		
Högl, 2011 <sup>1</sup>	35/166 (21.1)	60/163 (36.8)	19/166 (11.4)	23/163 (14.1)	120/166 (72.3)	106/163 (65.0)	17/166 (10.2)	15/163 (9.2)	8/166 (4.8)	3/163 (1.8)
Montagna, 2011 <sup>2</sup>	26/203 (12.8)	41/201 (20.4)	9/203 (4.4)	11/201 (5.5)	124/203 (61.1)	103/200 (51.5)	8/203 (3.9)	6/200 (3.0)		
Oertel, 2007 <sup>7</sup>	12/230 (5.2)	8/115 (7.0)	6/230 (2.6)	5/115 (4.3)	150/230 (65.2)	55/115 (47.8)	8/230 (3.5)	9/115 (7.8)	0/230 (0)	2/115 (1.7)
Winkelman, 2006 <sup>11</sup>	53/259 (20.5)	11/86 (12.8)	32/258 (12.4)	6/86 (7.0)	209/258 (81.0)	69/86 (80.2)	45/258 (17.4)	11/86 (12.8)		
<b>Ropinirole</b>										
Adler, 2004 <sup>8</sup>	2/22 (9.1)	1/22 (4.5)	1/22 (4.5)	1/22 (4.5)						
Bogan, 2006 <sup>9</sup>	23/187 (12.3)	26/194 (13.4)	7/187 (3.7)	9/194 (4.6)	155/187 (82.9)	129/193 (66.8)	33/187 (17.6)	20/193 (10.4)	0/187 (0)	1/193 (0.5)
Kushida, 2008 <sup>5</sup>	25/176 (14.2)	27/186 (14.5)	8/176 (4.5)	6/186 (3.2)	138/176 (78.4)	119/186 (64.0)			2/176 (1.1)	3/186 (1.6)
Montplaisir, 2006 <sup>10</sup>	15/45 (33.3)	28/47 (59.6)	1/45 (2.2)	0/47 (0)	26/45 (57.8)	24/47 (51.1)	6/45 (13.3)	6/47 (12.8)	0/45 (0)	2/47 (4.3)
Trenkwalder, 2004 <sup>12</sup>	35/147 (23.8)	30/139 (21.6)	16/147 (10.9)	6/139 (4.3)	120/146 (82.2)	103/138 (74.6)	34/146 (23.3)	21/138 (15.2)	3/146 (2.1)	4/138 (2.9)
Walters, 2004 <sup>13</sup>	29/131 (22.1)	29/136 (21.3)	11/131 (8.4)	9/136 (6.6)	112/131 (85.5)	102/136 (75.0)	32/131 (24.4)	24/136 (17.6)	2/131 (1.5)	5/136 (3.7)
<b>Rotigotine</b>										
Hening, 2010 <sup>26</sup>	152/404 (37.6)	33/100 (33.0)	82/404 (20.3)	4/100 (4.0)	355/404 (87.9)	84/100 (84.0)	79/404 (19.6)	12/100 (12.0)	17/404 (4.2)	4/100 (4.0)
Oertel, 2010 <sup>27</sup>	5/46 (10.9)	1/21 (4.8)	2/46 (4.3)	1/21 (4.8)	34/46 (73.9)	12/21 (57.1)	1/46 (2.2)	1/21 (4.8)		
Trenkwalder, 2008 <sup>6</sup>	96/341 (28.2)	49/117 (41.9)	54/341 (15.8)	8/117 (6.8)	265/341 (77.7)	64/117 (54.7)	50/341 (14.7)	9/117 (7.7)	25/341 (7.3)	5/117 (4.3)

**Appendix E. Table 2 Adverse effects for the dopamine agonist trials Part B**

Study	Fatigue n/N (%)		Nausea n/N (%)		Vomiting n/N (%)		Headache n/N (%)		Somnolence n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
<b>Pramipexole</b>										
Ferini-Stamb, 2008 <sup>4</sup>	16/182 (8.8)	4/187 (2.1)	32/182 (17.6)	11/187 (5.9)			27/182 (14.8)	24/187 (12.8)		
Högl, 2011 <sup>1</sup>	18/166 (10.8)	15/163 (9.2)	24/166 (14.5)	6/163 (3.7)			13/166 (7.8)	17/163 (10.4)	11/166 (6.6)	8/163 (4.9)
Montagna, 2011 <sup>2</sup>	16/203 (7.9)	8/200 (4.0)	28/203 (13.8)	13/200 (6.5)			21/203 (10.3)	19/200 (9.5)		
Oertel, 2007 <sup>7</sup>	21/230 (9.1)	7/115 (6.1)	28/230 (12.2)	7/115 (6.1)			30/230 (13.0)	11/115 (9.6)		
<b>Ropinirole</b>										
Adler, 2004 <sup>8</sup>			6/22 (27.3)	1/22 (4.5)	3/22 (13.6)	0/22 (0)	2/22 (9.1)	2/22 (9.1)	3/22 (13.6)	0/22 (0)
Bogan, 2006 <sup>9</sup>			80/187 (42.8)	15/193 (7.8)	16/187 (8.6)	3/193 (1.6)	31/187 (16.6)	36/193 (18.7)	24/187 (12.8)	13/193 (6.7)
Kushida, 2008 <sup>3</sup>			59/176 (33.5)	28/186 (15.1)	18/176 (10.2)	6/186 (3.2)	42/176 (23.9)	33/186 (17.7)	34/176 (19.3)	11/186 (5.9)
Montplaisir, 2006 <sup>10</sup>	38/202** (18.8)		8/45 (17.8); 101/202* (50.0)	1/47 (2.1)	31/202* (15.3)		5/45 (11.1); 44/202* (21.8)	3/47 (6.4)		
Trenkwalder, 2004 <sup>12</sup>			55/146 (37.7)	9/138 (6.5)	19/146 (13.0)	2/138 (1.4)	29/146 (19.9)	23/138 (16.7)	18/146 (12.3)	10/138 (7.2)
Walters, 2004 <sup>13</sup>	80/131 (61.1)	9/136 (6.6)	52/131 (39.7)	11/136 (8.1)	16/131 (12.2)	3/136 (2.2)	29/131 (22.1)	35/136 (25.7)		
<b>Rotigotine</b>										
Hening, 2010 <sup>26</sup>	27/404 (6.7)	4/100 (4.0)	73/404 (18.1)	10/100 (10.0)			47/404 (11.6)	8/100 (8.0)	47/404 (11.6)	6/100 (6.0)
Oertel, 2010 <sup>27</sup>			10/46 (21.7)	1/21 (4.8)			8/46 (17.4)	3/21 (14.3)	5/46 (10.9)	2/21 (9.5)
Trenkwalder, 2008 <sup>6</sup>	37/341 (10.9)	11/117 (9.4)	55/341 (16.1)	4/117 (3.4)			43/341 (12.6)	8/117 (6.8)		
Winkelman, 2006 <sup>11</sup>	13/258 (5.0)	4/86 (4.7)	49/258 (19.0)	4/86 (4.7)			46/258 (17.8)	15/86 (17.4)	26/258 (10.1)	4/86 (4.7)

\*Single-blind phase, all subjects received ropinirole.

**Appendix E. Table 3 Specific adverse effects for the dopamine agonist trials Part C**

Study	Application site reactions n/N (%)		Dizziness n/N (%)		Augmentation n/N (%)		Augmentation leading to study withdrawal n/N (%)		Withdrawal due to insufficient effect n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
<b>Pramipexole</b>										
Ferini-Stamb, 2008 <sup>4</sup>									5/182 (2.7)	33/187 (17.6)
Högl, 2011 <sup>1</sup>					18/152* (11.8)	14/149* (9.4)				
Montagna, 2011 <sup>2</sup>									7/203 (3.4)	20/201 (10.0)
Oertel, 2007 <sup>7</sup>			8/230 (3.5)	4/115 (3.5)						
Winkelman, 2006 <sup>11</sup>			25/258 (9.7)	6/86 (7.0)			1/259† (0.4)	1/86† (1.2)		
<b>Ropinirole</b>										
Adler, 2004 <sup>8</sup>			5/22 (22.7)	0/22 (0)					1/22 (4.5)	0/22 (0)
Bogan, 2006 <sup>9</sup>			18/187 (9.6)	11/193 (5.7)	3/187 (1.6)	1/193 (0.5)			2/187 (1.1)	5/193 (2.6)
Kushida, 2008 <sup>5</sup>										
Montplaisir, 2006 <sup>10</sup>			36/202** (17.8)						12/45 (26.7)	20/47 (42.6)
Trenkwalder, 2004 <sup>12</sup>									4/147 (2.7)	11/139 (7.9)
Walters, 2004 <sup>13</sup>			20/131 (15.3)	6/136 (4.4)					2/131 (1.5)	6/136 (4.4)
<b>Rotigotine</b>										
Hening, 2010 <sup>26</sup>	109/404 (27.0)	5/100 (5.0)	21/404 (5.2)	6/100 (6.0)					19/405 (4.7)	8/100 (8.0)
Oertel, 2010 <sup>27</sup>	8/46 (17.4)	1/21 (4.8)							1/46 (2.2)	0/21 (0)
Trenkwalder, 2008 <sup>6</sup>	145/341 (42.5)	2/117 (1.7)	18/341 (5.3)	3/117 (2.6)	ASRS§	0.30 (0.44)‡			22/341 (6.5)	37/117 (31.6)

\* Classified as augmentation cases. Among the 18 pramipexole cases, 14 were confirmed as augmentation and 4 were noted as having insufficient data for a definitive conformation. Among the 14 placebo cases, 9 were confirmed as augmentation and 5 were noted as having insufficient data for a definitive conformation.

\*\* Single-blind phase, all subjects received ropinirole.

† Defined as "worsened RLS."

§ASRS=Augmentation Severity Rating Scale. 1mg=0.31 (0.46), 2mg=0.24 (0.41), 3mg=0.25 (0.42)‡.

‡Mean (SD).

**Appendix E. Table 4 Withdrawals and adverse effects for the GABA analog trials Part A**

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1 serious adverse effects n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
<b>Gabapentin</b>										
Garcia-Borreguero, 2002 <sup>17</sup>	All patients** 3/24 (12.5), 1 during GABA phase and 2 during placebo phase		All patients** 1/24 (4.2) during placebo phase							
Kushida, 2009 <sup>16</sup>	14/114 (12.3)	16/108 (14.8)	10/114 (8.8)	3/108 (2.8)	93/113 (82.3)	80/108 (74.1)				
<b>Pregabalin</b>										
Allen, 2010 <sup>14</sup>	14/114 (12.3)	2/23 (8.7)	10/114 (8.8)	1/23 (4.3)	73/114 (64.0)	13/23 (56.5)	11 patients total*		1/114 (<1)	0/23
Garcia-Borreguero, 2010 <sup>15</sup>	6/30 (20.0)	9/28 (32.1)	4/30 (13.3)	0/28	25/30 (83.3)	9/28 (32.1)				

\* Not broken down by treatment arm; \*\* Crossover trial.

**Appendix E. Table 5 Adverse effects for the GABA analogs trials Part B**

Study	Somnolence n/N (%)		Dizziness n/N (%)		Dry mouth n/N (%)		Headache n/N (%)		Fatigue n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
<b>Pregabalin</b>										
Allen, 2010 <sup>14</sup>	18/114 (15.8)	1/23 (4.3)	16/114 (14.0)	1/23 (4.3)	6/114 (5.3)	0/23	15/114 (13.2)	3/23 (13.0)	9/114 (7.9)	0/23
Garcia-Borreguero, 2010 <sup>15</sup>	13/30 (43.3)	4/28 (14.3)	<i>Unsteadiness</i> 15/30 (50.0)	<i>Unsteadiness</i> 3/28 (10.7)	3/30 (10.0)	0/28	4/30 (13.3)	1/28 (3.6)		
<b>Gabapentin</b>										
Garcia-Borreguero,** 2002 <sup>17</sup>	2/23 (8.7)	0/24			1/23 (4.3)	0/24	0/23	1/24 (4.2)	<i>Malaise</i> 6/23 (26.1)	<i>Malaise</i> 2/24 (8.3)
Kushida,* 2009 <sup>16</sup>	Moderate 19/113 (16.8) Severe 0/113	Moderate 0/108 Severe 0/108	Moderate 11/113 (9.7) Severe 0/113	Moderate 1/108 (0.9) Severe 1/108 (0.9)			Moderate 8/113 (7.1) Severe 0/113	Moderate 4/108 (3.7) Severe 0/108	Moderate 5/113 (4.4) Severe 1/113 (0.9)	Moderate 0/108 Severe 0/108

\* Mild effects not reported here; \*\* Crossover trial.

**Appendix E. Table 6a Specific adverse effects for the GABA analog trials Part C**

Study	Vision effects n/N (%)		Nausea n/N (%)		Augmentation n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Allen, 2010 <sup>14</sup> (pregabalin)						
Garcia-Borreguero, 2010 <sup>15</sup> (pregabalin)	<i>Blurred vision</i> 3/30 (10.0)	<i>Blurred vision</i> 0/28	1/30 (3.3)	0/28	0/30	0/28
Kushida,* 2009 <sup>16</sup> (gabapentin)	<i>Dry eye</i> Moderate 1/113 (0.9)	<i>Dry eye</i> Moderate 0/108	Moderate 4/113 (3.5) Severe 0/113	Moderate 2/108 (1.9) Severe 0/108		
Garcia-Borreguero, 2002* <sup>17</sup> (gabapentin)	<i>Dry eye</i> 0/23	<i>Dry eye</i> 1/24 (4.2)	0/23	1/24 (4.2)	All patients 0/24	

\* Crossover study

**Appendix E. Table 6b Specific adverse effects for the GABA analog (pregabalin) trials Part C**

Study	Vision effects n/N (%)		Nausea n/N (%)		Augmentation n/N (%)		Dizziness n/N (%)		Headache n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Allen, 2010 <sup>14</sup>							16/114 (14.0)	1/23 (4.3)	15/114 (13.2)	3/23 (13.0)
Garcia-Borreguero, 2010 <sup>15</sup>	<i>Blurred vision</i> 3/30 (10.0)	<i>Blurred vision</i> 0/28 (0)	1/30 (3.3)	0/28 (0)	0/30 (0)	0/28 (0)				

\*Crossover study.

**Appendix E. Table 6c. Specific adverse effects for the GABA analog (gabapentin) trials Part C**

Study	Vision effects n/N (%)		Nausea n/N (%)		Augmentation n/N (%)		Dizziness n/N (%)		Headache n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Garcia-Borreguero, 2002* <sup>15</sup>	<i>Dry eye</i> 0/23 (0)	<i>Dry eye</i> 1/24 (4.2)	0/23 (0)	1/24 (4.2)	All patients 0/24 (0)					
Kushida,* 2009 <sup>16</sup>	<i>Dry eye</i> Moderate 1/113 (0.9)	<i>Dry eye</i> Moderate 0/108 (0)	Moderate 4/113 (3.5) Severe 0/113	Moderate 2/108 (1.9) Severe 0/108						

\*Crossover study.

**Appendix E. Table 7. Withdrawals and adverse effects for the dopamine agonist versus levodopa Part A**

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1 serious adverse effects n/N (%)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder 2007	74/178 (41.6)	83/183 (45.4)	47/178 (26.4)	47/183 (25.7)	148/178 (83.1)	142/183 (77.6)			12/178 (6.7)	9/183 (4.9)

**Appendix E. Table 8. Adverse effects for the dopamine agonist trials Part B**

Study	Fatigue n/N (%)		Nausea n/N (%)		Vomiting n/N (%)		Headache n/N (%)		Somnolence n/N (%)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder, 2007 <sup>18</sup>	22/178 (12.4)	8/183 (4.4)	55/178 (30.9)	19/183 (10.4)			24/178 (13.5)	17/183 (9.3)	19/178 (10.7)	7/183 (3.8)

**Appendix E. Table 9 Specific adverse effects for the dopamine agonist versus levodopa Part C**

Study	Application site reactions n/N (%)		Dizziness n/N (%)		Augmentation n/N (%)		Augmentation leading to study withdrawal n/N (%)		Withdrawal due to insufficient effect n/N (%)	
	Treatment	Control	Treatment	Treatment	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder, 2007 <sup>18</sup>			11/178 (6.2)	5/183 (2.7)	11/178 (6.2)	32/183 (17.5)	7/178 (3.9)	18/183 (9.8)	14/178 (7.9)	26/183 (14.2)

**Appendix E. Table 10. Withdrawals and adverse effects for the iron trials (secondary RLS)**

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Withdrawals due to lack of efficacy n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Adverse effects n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Grote, 2009 <sup>21</sup>	9/29 (31.0)	21/31 (67.7)	3/29 (10.3)	1/31 (3.2)	5/29 (17.2)	19/31 (61.3)	11/29 (37.9)	11/31 (35.5)	headache 4 effects* injection site rxn 1/29 (2.4)	headache 5 effects* injection site rxn 1/31 (3.2)
Wang, 2009 <sup>22</sup>	0/11	0/7	0/11	0/7	0/11	0/7	NR	NR	NR	NR

\* Not reported for unique patients

**Appendix E. Table 11. Adverse effects from observational studies and open-label extensions**

<b>Class of Drugs</b>	<b>Drug</b>	<b>Study (year)</b>	<b>Design</b>	<b>Duration (years)</b>	<b>Withdrawal from treatment</b>	<b>Reason for withdrawal (% of all withdrawals)</b>	<b>Adverse Effects</b>
<b>Anticonvulsant drug</b>	Gabapentin	Ellenbogen (2011)	Open-label extension to RCT	1	37% (187/573)	Lack of efficacy (5.8%); Adverse effects (34.2%); Other reasons (38%)	Somnolence, dizziness, headache, fatigue, nausea, condition aggravated, nasopharyngitis, upper respiratory tract infection,
<b>Opioids</b>	Multiple opioids [tilidine, dihydrocodeine, oxycodone, propoxyphene, methadone]	Walters (2001)	Retrospective	3.8 (mean, range 1 wk to 23 years)	44% (16/36)	Lack of efficacy (44%) Adverse effects (50%) Addiction and tolerance (6%)	Sleep apnea, daytime fatigue, migraine headache, grogginess, paradoxical hyperalerting response, constipation
	Methadone	Silver (2011)	Retrospective	10	15% (11/76) during the first year and 0% subsequently	Lack of efficacy Adverse effects	Specific adverse effects not reported
<b>Dopaminergic drug</b>	<b>Levodopa</b>	Högl (2011)	Prospective	0.5	42% (25/60)	Lack of efficacy (28%) Adverse effects (12%) Augmentation (28%) Other reasons (32%)	Fatigue, nausea, headache, condition aggravated, somnolence, nasopharyngitis, muscle spasms, arthralgia
	<b>Levodopa</b>	Trenkwalder, (2007)	RCT	1	45.4% (83/183)	Lack of efficacy (32%) Adverse effects (32%) Augmentation (22%) Other reasons (14%)	Nausea, constipation, headache, fatigue, somnolence, abdominal pain, vertigo, diarrhea, dizziness, nasopharyngitis, hypertension, hypotension, hyperhidrosis
	<b>Levodopa</b>	Trenkwalder (2003)	Open label extension of RCT	1	56% (13/23)	Lack of efficacy (7%); Adverse effects(7%); Augmentation (62%); Other reasons (23%);	Worsening of RLS symptoms, dry mouth, itching, persistent diarrhea
<b>Dopamine Agonists</b>	<b>Pramipexole</b>	Inoue, 2010	Open label extension of RCT	1	12.8% (18/141)	Adverse effects (44%) Other reasons (56%)	Nasopharyngitis, somnolence, headache, nausea, vomiting
	<b>Pramipexole</b>	Silber, 2003	Retrospective	1.2(mean)	25% (15/60)	Lack of efficacy (27%); Adverse effects (67%) Augmentation (6%) ;	Insomnia, nausea or dyspepsia, postural light headedness
	<b>Pramipexole</b>	Montplasil 2006	Retrospective	2.5 (mean)	22% (43/195)	Lack of efficacy (28%) Adverse effects (47%) Other reasons (25%)	Dizziness, nausea, sleepiness, insomnia
	<b>Pramipexole</b>	Silver, 2011	Retrospective	10	17% (28/164) during the first	Reason for discontinuation of treatment was side-effects in	Specific adverse effects not reported

					year and an annual rate of 9±3.9% for remaining years	the first year and RLS augmentation during subsequent years.	
	<b>Ropinirole</b>	Garcia-Borreguero (2007)	Open label extension of RCT	1	19% (59/310)	Lack of efficacy (19%) Adverse effects (44%)	Nausea, headache, arthralgia, nasopharyngitis, dizziness, back pain, vomiting, aggravation of symptoms, fatigue, somnolence
	<b>Rotigotine</b>	Trenkwalder (2008)	RCT	0.6	28% (96/341)	Lack of efficacy (23%); Adverse effects (54%); Other reasons (23%)	Skin reactions at application site, nausea, erythema, back pain, fatigue, pruritus, dizziness, arthralgia, headache, insomnia, hypertension, sleep disorder
	<b>Rotigotine</b>	Oertel (2011)	Open label extension of RCT	5	57% (169/295)	Lack of efficacy (18%) Adverse effects (53%) Other reasons (29%)	Application site reactions, insomnia, depression, nausea, fatigue, headache, dizziness, pulmonary fibrosis, obsessive compulsive disorder, sleep attack or sudden onset of sleep, syncope, nausea, sleep apnea
	<b>Multiple dopamine agonists [pramipexole; ropinirole; pergolide]</b>	Ondo (2004)	Retrospective	3.2 (mean, SD=1.7)	19% (10/52)	Lack of efficacy (20%) Adverse effects (20%) Augmentation (10%) Other reasons (50%)	Daytime sleepiness, nausea, peripheral edema, dizziness, light-headedness, gastrointestinal upset, constipation, headache, itchiness, rash.

# Appendix F

**Appendix F. Table 1. Summary of study baseline characteristics for dopamine agonist trials (n=14)**

Characteristic	Mean (range) <i>Unless otherwise note</i>	Number of trials reporting
Total number of patients evaluated	4254 (22 to 505)	14
Age of subjects, years	54.6 (50.9 to 60.0)	14
Women, %	64 (55 to 74)	14
Race/ethnicity, white %	96 (86 to 100)	7 <sup>g,i-n</sup>
RLS disease duration, years	8.8 (2.1 to 22.8)	12 <sup>a,b,d-l,n</sup>
Baseline IRLS total score (range 0 to 40)*	24.7 (22.0 to 28.1)	14
Patients with very severe disease, % (number of patients)	21.9 (8.5 to 37.1)	2 <sup>l,m</sup>
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	36.7 (21.8 to 72)	10 <sup>a,d,g-n</sup>
Patients who failed (experienced augmentation or rebound) with previous treatment, % (number of patients)	NR	NR**
Trials evaluating pramipexole, % (number of patients)	42 (1794)	5 <sup>g-k</sup>
Trials evaluating ropinirole, % (number of patients)	34 (1430)	6 <sup>a-f</sup>
Trials evaluating rotigotine (transdermal patch), % (number of patients)	24 (1030)	3 <sup>l-m</sup>
Crossover trials, % (number of patients)	0.5 (22)	1 <sup>a</sup>
Trial duration (double-blind phase), weeks	16 (6 to 29)	14
# of trials with a duration ≥6 months (% , number of patients)	3 <sup>h,l,m</sup> (35, n=1655)	
# of trials conducted in the Europe (% , number of patients)	7 <sup>f,h-k,m,n</sup> (53, n=2260)	
# of trials conducted in the US (% , number of patients)	5 <sup>a-c,g,l</sup> (38, n=1615)	
# of trials conducted in the Australia, Europe and North America, (% , number of patients)	2 <sup>d,e</sup> (9, n=379)	

\* IRLS = International Restless Legs Scale: Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40).

\*\* 2 pramipexole trials (Högl, Winkelman) and 5 ropinirole trials (Bogan, Kushida, Montplaisir, Trenkwalder 2004, Walters) reported augmentation/end-of-dose rebound during previous RLS treatment as an exclusion criterion.

a=Adler; b=Bogan; c=Kushida; d=Waters; e=Montplaisir; f=Trenkwalder 2004a; *Ropinirole*  
g=Winkelman; h=Högl; i=Montagna; j=Ferini-Strambi; k=Oertel 2007; *Pramipexole*  
l=Hening; m=Trenkwalder 2008; n= Oertel 2010. *Rotigotine*

**Appendix F. Table 2. Summary of study baseline characteristics for pramipexole trials**

Characteristic	Mean (range) <i>Unless otherwise note</i>	Number of trials reporting
Total number of patients evaluated	1794 (331 to 404)	5
Age of subjects, years	55.2 (51.4 to 56.9)	5
Women, %	65 (60 to 70)	5
Race/ethnicity, white %	95.2 (86.4 to 99.5)	4 <sup>a,c-e</sup>
RLS disease duration, years	4.9 (3.4 to 5.7)	5
Baseline IRLS total score (range 0 to 40)*	24.5 (23.5 to 25.9)	5
Patients with severe disease, % (ADD??)	( to)	
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	26.0 (21.8 to 30.8)	5
Trial duration (double-blind phase), weeks	13.4 (6 to 26)	5
Trials with a duration ≥6 months, % (number of patients)	18 (331)	1 <sup>b</sup>
Trials conducted in the Europe, % (number of patients)	81 (1449)	4 <sup>b-e</sup>
Trials conducted in the US, % (number of patients)	19 (345)	1 <sup>a</sup>
Trials conducted in the Australia, Europe and North America, % (number of patients)	none	-

IRLS = International Restless Legs Scale

a=Winkelman; b=Högl; c=Montagna; d=Ferini-Strambi; e=Oertel 2007.

Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

**Appendix F. Table 3. Summary of study baseline characteristics for ropinirole trials**

Characteristic	Mean (range) <i>Unless otherwise note</i>	Number of trials reporting
Total number of patients evaluated	1430 (22 to 381)	6
Age of subjects, years	53.3 (50.9 to 60)	6
Women, %	61 (55 to 73)	6
Race/ethnicity, white %	NR	0
RLS disease duration, years	19.1 (16.8 to 22.8)	5 <sup>a,b,d,e,f</sup>
Baseline IRLS total score (range 0 to 40)*	24.3 (22 to 26)	6
Patients with severe disease, % (ADD??)	( to)	
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	44.3 (40.9 to 44.6)	2 <sup>a,d</sup>
Trial duration (double-blind phase), weeks	11.9 (8 to 12)	6
Trials with a duration ≥6 months	none	-
Trials conducted in the Europe, % (number of patients)	20 (286)	1 <sup>f</sup>
Trials conducted in the US, % (number of patients)	53 (765)	3 <sup>a-c</sup>
Trials conducted in the Australia, Europe and North America, % (number of patients)	27 (379)	2 <sup>d,e</sup>

IRLS = International Restless Legs Scale

a=Adler; b=Bogan; c=Kushida; d=Waters; e=Montplaisir; f=Trenkwalder 2004a.

\* Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

**Appendix F. Table 4. Summary of study baseline characteristics for rotigotine trials**

<b>Characteristic</b>	<b>Mean (range) Unless otherwise note</b>	<b>Number of trials reporting</b>
Total number of patients evaluated	1030 (67 to 505)	3
Age of subjects, years	55.2 (52.4 to 59.4)	3
Women, %	67 (60 to 74)	3
Race/ethnicity, white %	97 (94 to 100)	3
RLS disease duration, years	2.1 (2.1 to 2.2)	2 <sup>a,c</sup>
Baseline IRLS total score (range 0 to 40)*	25.6 (23.3 to 28.1)	3
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	53.3 (35.8 to 72)	3
Trial duration (double-blind phase), weeks	26.1 (7 to 29)	3
Trials with a duration ≥6 months, % (number of patients)	93 (963)	2 <sup>a,b</sup>
Trials conducted in the Europe, % (number of patients)	51 (525)	2 <sup>b,c</sup>
Trials conducted in the US, % (number of patients)	49 (505)	1 <sup>a</sup>
Trials conducted in the Australia, Europe and North America, % (number of patients)	none	-

IRLS = International Restless Legs Scale

a=Hening; b=Trenkwalder 2008; c=Oertel 2010.

\* Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

# **Appendix G**

**Appendix G. Table 1. Individual Study Quality for the Dopamine agonist trials**

Study	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Högl, 2011 <sup>1</sup>	Unclear	Double*	No, treatment and post-baseline data** required (10 excluded, 3%)	No, only due to adverse effects	Fair
Montagna, 2011 <sup>2</sup>	Unclear†	Double*	No, treatment and post-baseline data required (2 excluded, <1%)	Yes	Good
Hening, 2010 <sup>26</sup>	Adequate	Double	No, post-baseline data** required (11 excluded, 2%)	Yes	Good
Oertel, 2010 <sup>27</sup>	Adequate	Double	No, 1 excluded	Yes	Good
Ferini-Stambi, 2008 <sup>4</sup>	Adequate	Double*	No, treatment and post-baseline data required (12 excluded, 3%)	Yes	Good
Kushida, 2008 <sup>3</sup>	Unclear	Double	No, post-baseline data** required (3 excluded, <1%)	No, only due to adverse effects	Fair
Trenkwalder, 2008 <sup>6</sup>	Adequate	Double	No, post-baseline data** required (11 excluded, 2%)	Yes	Good
Oertel, 2007 <sup>7</sup>	Unclear†	Double	No, treatment and post-baseline data required (7 excluded, 2%)	Yes	Good
Bogan, 2006 <sup>9</sup>	Adequate	Double*	No, treatment required (1 excluded, <1%)	Yes	Good
Montplaisir, 2006 <sup>10</sup>	Adequate	Double*	Yes	Yes	Good
Winkelman, 2006 <sup>11</sup>	Adequate	Double	No, post-baseline data required (5 excluded, 1%)	Yes	Good
Adler, 2004 <sup>8</sup>	Adequate	Double	Yes	Yes	Good
Trenkwalder, 2004 <sup>12</sup>	Adequate	Double*	No, treatment required (2 excluded, <1%)	Yes	Good
Walters, 2004 <sup>13</sup>	Adequate*	Double	Yes	Yes	Good

Double blinding denotes participants and investigators

\*plus study team personnel and/or end points adjudicated by blinded committee

\*\* primary efficacy outcome

† noted as adequate based on information in a Cochrane systematic review (ref). This information was not evident in the trial publication but is presumed to have been obtained directly from the study sponsor.

**Appendix G. Table 2. Individual Study Quality for the GABA analog trials**

<b>Study</b>	<b>Allocation concealment</b>	<b>Blinding</b>	<b>Intention-to treat analyses</b>	<b>Withdrawals adequately described</b>	<b>Quality</b>
Allen, 2010 <sup>14</sup>	Adequate	Double	Yes	Yes	Good
Garcia-Borreguero, 2010 <sup>15</sup>	Adequate	Double	Yes	Yes	Good
Kushida, 2009 <sup>16</sup>	Unclear	Double	No, treatment and post-baseline data required (2 excluded, <1%)	Yes	Fair
Garcia-Borreguero, 2002 <sup>17</sup>	Adequate	Double	No, treatment required (2 excluded from each phase* 8.3%)	Yes	Good

Double blinding denotes participants and investigators

\*crossover trial.

**Appendix G. Table 3. Individual Study Quality for the iron and miscellaneous trials**

<b>Study /Intervention</b>	<b>Allocation concealment</b>	<b>Blinding</b>	<b>Intention-to treat analyses</b>	<b>Withdrawals adequately described</b>	<b>Quality</b>
Grote, 2009 <sup>21</sup> Iron	Adequate	Double	Yes	Yes	Good
Wang, 2009 <sup>22</sup> Iron	Adequate	Double	Yes	Yes (none withdrew)	Good
Cuellar, 2009 <sup>23</sup> Valerian	Adequate	Double*	No, study completers only (11 excluded, 23%)	Yes	Fair
Lettieri, 2009 <sup>24</sup> Compression device	Adequate	Double*	Yes	Yes	Good
Aukerman, 2006 <sup>25</sup> Exercise	Unclear	NR	No, 13 patients (32%) were unable to participate	Partially	Fair

Double blinding denotes participants and investigators

\* Plus additional study personnel

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