

## Appendix A. Search Strategies

### Database: Ovid MEDLINE(R) without Revisions

#### KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"
10. limit 9 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or multicenter study or randomized controlled trial)
11. 9 and random\$.mp.
12. 10 or 11

#### KQ 2a: Supplemental Search – Abuse and Addiction Detection

1. Analgesics, Opioid/
2. 1 and 2
3. Substance Abuse Detection/
4. Opioid-Related Disorders/ or Substance-Related Disorders/
5. 3 and (4 or 5)
6. (chronic adj3 pain).mp.
7. 1 and 7
8. 8 not 3
9. 9 and (4 or 5)
10. 6 or 10

#### KQ 3a-3g; 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid\*.mp. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or

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- phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. or/1-3
  4. Opioid-Related Disorders/
  5. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
  6. Drug Administration Schedule/
  7. Pain Management/
  8. Clinical Protocols/
  9. Breakthrough Pain/
  10. Dose-Response Relationship, Drug/
  11. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
  12. exp Chronic Pain/
  13. (chronic adj2 pain).mp.
  14. or/4-6
  15. or/7-12
  16. 15 and 16
  17. (or/13-14) and 17
  18. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
  19. limit 19 to yr="2008 - 2013"

### **KQ 3h: Dosing Strategies – Tapered Dosing**

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17

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19. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper\$ or decreas\$ or reduc\$).mp.
21. limit 20 to yr="1902 - 2007"

### **KQ 4a-4b: Risk Prediction**

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10
12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict\$ or assess\$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

### **KQ 4c: Risk Mitigation**

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or

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- phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
  5. exp Chronic Pain/
  6. (chronic adj2 pain).mp.
  7. Opioid-Related Disorders/
  8. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
  9. 4 and (5 or 6)
  10. 7 or 8
  11. 9 or 10
  12. Patient Compliance/
  13. Health Services Misuse/
  14. Substance Abuse Detection/
  15. Drug Monitoring/
  16. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
  17. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
  18. (opioid\$ adj7 (contract\$ or agree\$)).mp.
  19. Contracts/
  20. Patient Education as Topic/
  21. Drug Overdose/
  22. or/12-21
  23. ((risk\$ adj7 mitigat\$) or reduc\$).mp.
  24. ("risk evaluation and mitigation" or "rems").mp.
  25. Risk Reduction Behavior/ or Risk/
  26. or/23-25
  27. 11 and 22 and 26
  28. limit 27 to yr="2008 - 2013"

### **KQ 4d: Treatment Strategies**

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
7. Patient Compliance/
8. Health Services Misuse/
9. Substance Abuse Detection/
10. Drug Monitoring/

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11. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
12. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
13. (opioid\$ adj7 (contract\$ or agree\$)).mp.
14. Contracts/
15. Patient Education as Topic/
16. Drug Overdose/
17. or/7-16
18. Substance Abuse Detection/
19. Opiate Substitution Treatment/
20. Risk Management/
21. or/18-20
22. or/4-6
23. 17 and 21 and 22
24. treatment outcome.mp. or Treatment Outcome/
25. (treatment and (strateg\$ or plan\$)).mp.
26. 23 and (24 or 25)

### All KQs: Systematic Reviews

1. meta-analysis.mp. or exp Meta-Analysis/
2. (cochrane or medline).tw.
3. search\$.tw.
4. 1 or 2 or 3
5. "Review Literature as Topic"/ or systematic review.mp.
6. 4 or 5
7. exp Analgesics, Opioid/
8. opioid\*.mp.
9. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
10. 10 (chronic and pain).mp.
11. or/7-9
12. 6 and 10 and 11
13. limit 12 to yr="2008 - 2013"

### Database: EBM Reviews - Cochrane Central Register of Controlled Trials

### KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid\*.mp.

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3. (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"

### KQ 3a-3g, 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. limit 18 to yr="2008 - 2013"

### KQ 3h: Tapered Dosing

1. exp Analgesics, Opioid/
2. opioid\*.mp.

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3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper\$ or decreas\$ or reduc\$).mp.
21. limit 20 to yr="1902 - 2007"

### ***KQ 4a-b: Risk Prediction***

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10

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12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict\$ or assess\$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

### KQ 4c: Risk Mitigation

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (20690)
4. or/1-3 (22725)
5. exp Chronic Pain/ (79)
6. (chronic adj2 pain).mp. (2585)
7. Opioid-Related Disorders/ (571)
8. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp. (116)
9. 4 and (5 or 6) (523)
10. 7 or 8 (630)
11. 9 or 10 (1139)
12. Patient Compliance/
13. Health Services Misuse/
14. Substance Abuse Detection/
15. Drug Monitoring/
16. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
17. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
18. (opioid\$ adj7 (contract\$ or agree\$)).mp.
19. Contracts/
20. Patient Education as Topic/
21. Drug Overdose/
22. or/12-21
23. ((risk\$ adj7 mitigat\$) or reduc\$).mp.
24. ("risk evaluation and mitigation" or "rems").mp.

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25. Risk Reduction Behavior/ or Risk/
26. or/23-25
27. 11 and 22 and 26
28. limit 27 to yr="2008 - 2013"

### **KQ 4d: Treatment Strategies**

1. exp Analgesics, Opioid/
2. opioid\*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict\* or misuse or diversion)).mp.
7. Patient Compliance/
8. Health Services Misuse/
9. Substance Abuse Detection/
10. Drug Monitoring/
11. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
12. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
13. (opioid\$ adj7 (contract\$ or agree\$)).mp.
14. Contracts/
15. Patient Education as Topic/
16. Drug Overdose/
17. or/7-16
18. Substance Abuse Detection/
19. Opiate Substitution Treatment/
20. Risk Management/
21. or/18-20
22. or/4-6
23. 17 and 21 and 22
24. treatment outcome.mp. or Treatment Outcome/
25. (treatment and (strateg\$ or plan\$)).mp.
26. 23 and (24 or 25)

### **Database: PsycINFO**

### **KQ 1 and 2: Comparative Effectiveness and Harms**

1. opioid\*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or

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dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.

3. (chronic and pain).mp.
4. (1 or 2) and 3
5. (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
6. 4 and 5
7. limit 6 to yr="2008 - 2014"
8. limit 7 to human

### KQ 3a-3g, 3i: Dosing Strategies

1. opioid\*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (dose or dosing or dosage).mp.
6. limit 5 to human
7. limit 6 to yr="2008 - 2014"

### KQ 3h: Tapered Dosing

1. opioid\*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (taper\$ or decreas\$).mp.
6. limit 5 to human

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### KQ 4a-4c: Risk Prediction and Mitigation

1. opioid\*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. risk.mp.
6. 4 and
7. limit 6 to human
8. limit 7 to yr="2008 - 2014"

### KQ 4d: Treatment Strategies

1. opioid\*.mp
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp
3. (chronic and pain).mp
4. (1 or 2) and 3
5. 4 and ((treatment and (strateg\$ or plan\$).mp
6. 5 and (overdose or abuse or misuse or pain or function or "quality of life" or "qol").mp
7. limit 6 to human

### Database: EBSCO CINAHL Plus with Full Text

#### All Key Questions (except 3h, 4d)

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

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- "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
- (MH "Chronic Pain") OR "chronic pain"
  - 1 and 2
  - "random\*" OR "control\*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
  - 3 and 4
  - Limit 4 to published date 20080101-20131015

### KQ 3h: Tapered Dosing

- (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphan" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
- (MH "Chronic Pain") OR "chronic pain"
- 1 and 2
- "random\*" OR "control\*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
- 3 and 4
- "taper\*" OR "decreas\*"
- 5 and 6
- Limit 6 to published date 19920101-20071231

### KQ 4d: Treatment Strategies

- (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphan" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

## Appendix A. Search Strategies

"meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"

2. (MH "Chronic Pain") OR "chronic pain"
3. 1 and 2
4. "random\*" OR "control\*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
5. 3 and 4
6. "treatment" AND ("strateg\*" OR "plan\*")
7. 5 and 6
8. Limit 7 to published date 19920101-20071231

## Database: EBM Reviews – Cochrane Database of Systematic Reviews

### All KQs: Systematic Reviews

1. (opioid\$ or alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).ti.
2. 1 and (chronic and pain).mp.
3. limit 2 to full systematic reviews

## Appendix B. PICOTS

PICOT	Include	Exclude
Population and Conditions of Interest	<ul style="list-style-type: none"> <li>For all KQs: Adults (age &gt;18 years) with various types of chronic pain (defined as pain lasting &gt;3 months), including patients with acute exacerbations of chronic pain (KQ 1g)</li> <li>For KQs 1b, 2b: Subgroups as defined by specific pain condition, patient demographics (e.g., age, race, ethnicity, sex), comorbidities (including medical comorbidities and mental health disorders, including past or current alcohol or substance abuse and related disorders, and those at high risk for addiction);</li> <li>For KQ 2b: Subgroups also defined by the dose of opioids used</li> </ul>	<ul style="list-style-type: none"> <li>Patients with pain at end of life, acute pain, pregnant or breastfeeding, patients treated with opioids for addiction</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>For KQs 1, 2, 3: Long- or short-acting opioids (including tapentadol) used as long-term therapy (defined as use of opioids on most days for &gt;3months)</li> <li>For KQ 1d: Also include combination of opioid plus nonopioid therapy (pharmacological or nonpharmacological)</li> <li>For KQ 1Va, b: Risk prediction instruments</li> <li>For KQ 1Vc: Opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse deterrent formulations</li> <li>For KQ 1Vd: Opioid management strategies</li> </ul>	<ul style="list-style-type: none"> <li>Intravenous or intramuscular administration of opioids</li> <li>Tramadol</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>For KQs 1a, 1b, 2a, 2b: Opioid vs. placebo or nonopioid therapy (including usual care)</li> <li>For KQ 1c: Opioid vs. nonopioid therapy (pharmacological or nonpharmacological [e.g., exercise therapy, cognitive behavioral therapy, interdisciplinary rehabilitation])</li> <li>For KQ 1d: Opioid plus nonopioid therapy (pharmacological or nonpharmacological) vs. opioid or nonopioid therapy alone</li> <li>For KQ 3a: Comparisons of different dose initiation and titration strategies</li> <li>For KQ 3b: Short- vs. long-acting opioids</li> <li>For KQ 3c: One long-acting opioid vs. another long-acting opioid</li> <li>For KQ 3d: Short- plus long-acting opioid vs. long-acting opioid</li> <li>For KQ 3e: Scheduled, continuous vs. as-needed dosing of opioid</li> <li>For KQ 3f: Dose escalation vs. dose maintenance or use of maximum dosing thresholds</li> <li>For KQ 3g: Opioid rotation vs. continuation of current opioid</li> <li>For KQ 3h: Comparisons of different methods for treating acute exacerbations of chronic pain</li> <li>For KQ 3i: Decreasing or tapering opioid doses vs. continuation of opioids</li> <li>For KQ 3j: Comparisons of different tapering protocols and strategies</li> <li>For KQ 4a: Risk prediction instruments vs. reference standard for overdose or opioid addiction, abuse or misuse</li> <li>For KQ 4b: Risk prediction instruments vs. nonuse of risk prediction instruments</li> <li>For KQ 4c: Risk mitigation strategies (see Interventions above) vs. nonuse of risk mitigation strategies</li> <li>For KQ 4d: Comparisons of treatment strategies for managing patients with addiction to prescription opioids</li> </ul>	

## Appendix B. PICOTS

PICOT	Include	Exclude
Outcomes	<ul style="list-style-type: none"> <li>For KQs 1, 3, 4: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression), doses of opioids used</li> <li>Also for KQs 2, 3, 4: Overdose, opioid use disorder, addiction, abuse, and misuse; other opioid-related harms (including gastrointestinal, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression))</li> </ul>	<ul style="list-style-type: none"> <li>Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)</li> </ul>
Timing	<ul style="list-style-type: none"> <li>Any duration for outcomes related to overdose and injuries (falls, fractures, motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy</li> <li>For other outcomes: &gt;1 year</li> </ul>	
Setting	<ul style="list-style-type: none"> <li>Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)</li> </ul>	<ul style="list-style-type: none"> <li>Addiction treatment settings, inpatient settings</li> </ul>
Study Design	<ul style="list-style-type: none"> <li>For all KQs, randomized controlled trials, controlled cohort studies, and case-control studies (controlled observational studies must have performed adjustment on potential confounders)</li> <li>For all KQs, we excluded uncontrolled observational studies, case series, and case reports, with the exception of KQ 2a for which we included uncontrolled observational studies of patients with chronic pain prescribed long-term opioid therapy for at least one year that used predefined methods to assess rates of abuse, misuse, or addiction</li> <li>For KQ 4a, we included studies that evaluated the predictive ability of risk prediction instruments, and excluded studies that did not evaluate the performance of a risk prediction instrument against a reference standard.</li> </ul>	

KQ, key question; PICOT=populations, interventions, comparators, outcomes, timing, setting.

## Appendix C. Included Studies\*

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- Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. *Spine.* 2005;30(22):2484-90. PMID: 16284584.
- Ashburn MA, Slevin KA, Messina J, et al. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. *Anesth Analg.* 2011;112(3):693-702. PMID: 21304148.
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- Carman WJ, Su S, Cook SF, et al. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Drug Saf.* 2011;20(7):754-62. PMID: 21567652.
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## Appendix C. Included Studies\*

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**\*Appendix C is the reference list for all appendixes.**

## Appendix D. Excluded Studies

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## Appendix D. Excluded Studies

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## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Banta-Green, 2009	Retrospective cohort Integrated group health system United States	Patients aged 21-79 with chronic opioid prescriptions over at least 3 years (filling $\geq 10$ opioid prescriptions in a 12-month period or filling a prescription for at least a 120-day supply and $\geq 6$ prescriptions in a 12-month period) Exclude: patients with cancers other than benign, nonmelanoma skin cancer	n=704 Mean age: 55 years Female sex: 62% Race: 89% White	Dose: mean 50 mg/day MED Duration: NR Indication: NR	Factor scores based on DSM-IV and PDUQ criteria UDT: not specified	Opioid dependence: 13% (91/704) Opioid abuse without dependence: 8% (56/704)	Fair
Boscarino, 2010	Cross-sectional study, outpatients from nine primary care (83%) and 3 specialty clinics (17%), based on 1 year of observation	$\geq 4$ physician orders for opioid therapy in past 12 mos., identified from E.H.R.; mean prescriptions=10.7 Exclude: cancer	n=705 Age: 18-64: 79% 65+: 21% Female sex: 61% White race: 98%	Dose: NR Duration: mean of 10.7 prescriptions over 1 year Indication: noncancer, otherwise not described	Diagnostic interview: CIDI; DSM-IV criteria for opioid dependence	25.8% (95% CI: 22.0-29.9) met criteria for current opioid dependence; 35.5% (95% CI: 31.1-40.2) met criteria for lifetime dependence Factors associated with dependence: Age <65 years (OR 2.3, 95% CI 1.6 to 3.5) History of opioid abuse (OR 3.8, 95% CI 2.6 to 5.7) History of high dependence severity (OR 1.8, 95% CI 1.4 to 2.5) History of major depression (OR 1.3, 95% CI 1.0 to 1.6), Current use of psychotropic medications (OR 1.7, 95% CI 1.2 to 2.5)	Fair

## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Carrington Reid, 2002	Retrospective cohort Two primary care centers United States	Patients who received $\geq 6$ months of opioid prescriptions during a 1- year period for noncancer pain and were not on methadone maintenance.	n=98 (50 at VA and 48 at urban primary care clinic)  VA site vs. urban primary care site Median age: 54 vs. 55 years Female sex: 8% vs. 67% Race: 88% White, 12% Black vs. 52% White, 36% Black, 10% Hispanic Mean duration of pain: 10 vs. 13 years	VA site vs. urban primary care site Dose: NR Duration: NR Indication: 44% low back, 10% injury- related, 8% diabetic neuropathy, 16% degenerative joint disease, 4% headache, 10% spinal stenosis vs. 25% low back pain, 13% injury-related, 10% diabetic neuropathy, 13% degenerative joint disease, 13% headache, 4% spinal stenosis	Chart review for lost or stolen opioids, documented use of other sources to obtain opioids, and requests for $\geq 2$ early refills UDT: not specified	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time of onset of abuse behaviors: 24 months Factors associated with decreased risk of opioid abuse behaviors: No history of substance use disorder (adjusted OR 0.72, 95% CI 0.45 to 1.1) Age (adjusted OR 0.94, 95% CI 0.94 to 0.99)	Fair
Compton, 2008	Prospective cohort VA pain clinic United States One year	Consecutive chronic nonmalignant pain patients receiving opioids Exclude: patients with diagnosed substance use disorder	n=135 Mean age: 53 years Female sex: 6% Race: NR Baseline VAS score: 6.75	Dose: NR Duration: NR Indication: 77% musculoskeletal, 19% neuropathic, 4% multicategory	Chart review for opioid discontinuation due to medication agreement violation (including for opioid misuse or abuse) UDT: not specified	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135) Overdose deaths: none reported	Fair

## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Cowan, 2003	Cross-sectional Pain clinic United Kingdom	Patients attending pain clinic and receiving controlled-release oral morphine sulfate or transdermal fentanyl	n=104 Mean age: 55.4 years Female sex: 39% Race: NR Mean duration of pain: 10.5 years	Dose: NR Duration: mean 14.1 months Indication: 34% degenerative disease, 24% failed back/neck surgery syndrome, 10% complex regional pain syndrome, 10% osteoarthritis	SUQ UDT: not specified	Self-reported addiction: 1.9% (2/104) Craving opioids: 2.9% (3/104) Has taken drugs to enhance the effect of opioids: 0.9% (1/104) Has used alcohol to enhance the effect of opioids: 0.9% (1/104)	Fair
Fleming, 2007 See also: Saffier, 2007	Primary care practices of 235 physicians	Daily opioids over past 3 months; n=801 96% had received opioids for 12 months Exclusions: cancer pain	Mean Age: 48.6 Female sex: 68% Race: 75.6% White; 23.1% African American; 1% other Disability income: 48%	Mean daily dose: 92 MEQ/d Duration: ≥12 mos. For 96% Indication: Osteoarthritis: 24%; low back pain, herniated disc or stenosis: 25%; migraine 8%; neuropathy 5%	In person interviews with ASI; SDSS; Aberrant Behavior 12-item List UDT: collected at end of interview	Met DSM-4 criteria for opioid dependence: 3.1% Met DSM-4 criteria for opioid abuse: 0.6% Any illicit drug on UDS: 24% (mostly marijuana) Aberrant behaviors: purposely oversedated: 24% (186/785) Felt intoxicated from pain med: 33% (260/785) Requested early refills: 45% (359/785) Increased dose on own: 37% (288/785) Meds lost or stolen: 30% (236/785) Used opioid purpose other than pain: 16% (125/785) Drank alcohol to relieve pain: 20% (154/785)	Fair

## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Hojsted, 2010	Cross-sectional Pain clinic Denmark	Adults with chronic noncancer pain Exclude: patients suffering from cognitive dysfunction, in poor health due to other condition, or did not use any pain medication	n=253, of which 187 were receiving opioid therapy (207 total and 153 receiving opioids returned questionnaire) Mean age: 52 years Female sex: 64% Race: NR Mean pain score: NR Receiving opioids: 74% (187/253) Indication: 93% noncancer pain, 7% cancer pain	Dose: NR Duration: mean 6.8 years (among those who completed questionnaire, n=207) Indication: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; a positive screen by either provider was considered positive UDT: not specified	Addiction to opioids or hypnotics, ICD-10: 11.1% (28/253) Addiction to opioids, ICD-10: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria: 14.6% (37/253) Addiction to opioids, Portenoy's Criteria: 19.3% (36/187) Overdose deaths: NA	Fair

## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Portenoy, 2007	Prospective registry study 35 pain clinics United States Three years (mean duration 23.8 months)	Adult patients who had participated in any of five previous CCTs of CR oxycodone for noncancer pain	n=227 Mean age: 56 years Female sex: 57% Race: 90% White BPI average pain score: 6.4	Dose: mean 52.5 mg/day Duration: mean 541.5 days Indication: 38% osteoarthritis, 31% diabetic neuropathy, 31% low back pain	Physician- completed brief questionnaire assessing problematic drug- related behavior with verification by an independent panel of experts UDT: not specified	Problematic drug-related behavior identified by physicians: 5.7% (13/227) Problematic drug-related behavior adjudicated by expert panel as positive and meeting DSM-IV criteria: 0 Problematic drug-related behavior adjudicated by expert panel as positive: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as withdrawal: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as alleged: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as negative: 0.4% (1/227) Overdose deaths: 1 (phenylpropanolamine, oxycodone, and alcohol)	Fair

## Appendix E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Schneider, 2010	Chart review Single center pain clinic United States	Patients receiving opioid therapy for ≥1 year	n=197 Mean age: 49 years Female sex: 67% Race: NR	Dose: mean 180 mg/day MED (long acting), 49 mg/day MED (short acting) Duration: mean 4.7 years Indication: 51% back pain, 10% neck pain, 9% fibromyalgia, 8% other myofascial pain	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT: 8.7% (14/161) Aberrant drug-related behaviors noted in chart: 15.7% (31/197)	Fair
Wasan, 2009	Cross-sectional 5 pain clinics United States	Patients with noncancer chronic pain receiving opioid therapy	n=622 Mean age: 50.4 years Female sex: 55% Race: 80% White Mean pain score: 5.96	Dose: NR Duration: mean 6.2 years Indication: 61% low back pain	POTQ, PUDQ, and UDT	Positive scores of ≥2 on POTQ: 24% (115/480) Score ≥11 on PDUQ: 29.1% (130/447) Positive UDT: 37.1% (134/356)	Fair

Note: The references are located in Appendix C.

ASI=Addiction Severity Index; CCT=case control trial; CR=case report; CI=confidence interval; CIDI= Composite International Diagnostic Interview; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-V=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GC/MS= Gas Chromatography with Mass Spectrometry confirmatory test; ICD-10=International Statistical Classification of Diseases and Related Health Problems, tenth revision; MED=morphine equivalent dose; MEQ/d=milliequivalent/hydrogen; NR=not relevant; PDUQ= Prescription Drug Use Questionnaire; POTQ=Prescription opioid therapy questionnaire; SDSS= Substance dependence severity scale; UDT=urine drug testing; VA=Veterans Administration; VAS= Visual Analog Scale

## Appendix E2. Observational Studies of Long-term Opioid Use and Overdose

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Dunn, 2010	KQ2a, b	Retro-spective cohort (Group Health) United States	Age > 18 years starting new episode of opioid use (no opioids in past 6 mos) from 1997 -2005; having 3 or more opioid scripts filled in first 90 days of episode; diagnosis of chronic noncancer pain in 2 wks before first opioid script.	Morphine equivalent doses: A. 1-<20 mg/day B. 20-<49 mg/day C. 50-<99 mg/day D. >=100 mg/day	Mean (SD; range) age (years): 54 (16.8; 18-99) Female sex: 59.6% Race: NR Smoking: 29.5% Depression: 26.9% Substance abuse: 6.2% Charlson Score, mean (SD; range): 0.71 (1.48;0-14) Pain diagnosis: 37.9% back; 30.3% extremity; 12.7% osteoarthritis; 12.3% injury, contusion, or fracture;8.9% neck Opioid dose, mean (median): 13.3 mg (6.0 mg) Sedative-hypnotic use, any: 74.7% Muscle relaxant: 52.3% Benzodiazepine: 42.7% Opioid: Hydrocodone: 46.3% Oxycodone: 24.5% Codeine combination: 11.6% Long-acting morphine: 6.2% Any short acting opioid: 90.4% Any long-acting opioid: 9.6%	All patients in HMO meeting inclusion criteria

## Appendix E2. Observational Studies of Long-term Opioid Use and Overdose

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Dunn, 2010	Screened: Not reported Eligible: Not reported Enrolled: 9,940 Mean duration of follow-up (range): 42 mos (<1-119); Analyzed: All included in analysis Loss to followup: 61% had complete followup from cohort entry until end of study or event occurred; 32% left GHC during study; 7% died	Sedative-hypnotic use as time-varying covariate Age Sex Smoking Depression diagnosis Substance abuse diagnosis Index pain diagnosis Chronic disease comorbidity adjustors (RxRisk & Charlson)	51 patients with overdose events (148 per 100,000 person-years); 40 serious overdose events (116 per 100,000 person-years); 6 fatal overdose events (17 per 100,000 person-years)  Rate of any overdose per 100,000 person-years (95% CI); HR (95% CI) No opioid: 36 (13-70); 0.31 (0.12-0.80); 6 overdose events A. (referent): 160 (100-233); 1.0 B. 260 (95-505); 1.44 (0.57-3.62) C. 677 (249-1317); 3.73 (1.47-9.5) D. 1791 (894-2995); 8.87 (3.99-19.72) Opioid dose, any: 256 (187-336); 5.16 (2.14-12.48); 45 overdose events  HR, serious events (95% CI) No opioid: 0.19 (0.05-0.68); A. (referent): 1.0 B. 1.19 (0.4-3.6); C. 3.11 (1.01-9.51); D. 11.18 (4.8-26.03); Opioid dose, any: 8.39 (2.52-27.98)	National Institute of Drug Abuse and Wellcome Trust	Fair

## Appendix E2. Observational Studies of Long-term Opioid Use and Overdose

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Gomes, 2011	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid for nonmalignant pain (1997-2006)	Cases: Died of an opioid-related cause (n=498 matched a control) Controls: received opioids (n=1714) A. 1-<20 mg/day B. 20-<50 mg/day C. 50-<100 mg/day D. 100-<200 mg/day E. >=200 mg/day	Total cohort n= 607,156 Mean age (years): 44.49 vs 44.72 Gender (not reported which one): 58.8% vs 58.0%	Controls matched on disease risk index (0.2 standard deviation caliper), age, gender, index year, and Charlson

Note: The references are located in Appendix C.

CI=confidence interval; EtOH=ethanol; GHC=Group Health Cooperative; HMO=Health Maintenance Organization; HR=hazard ratio; ICES= Institute for Clinical Evaluative Sciences; MOHLTC= Ontario Ministry of Health and Long-Term Care; NR=not relevant; RxRisk=drug index for prescription drugs.

## Appendix E2. Observational Studies of Long-term Opioid Use and Overdose

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2011	Screened: 1463 Eligible: 1179 Primary-analysis: 593 with 498 matched Secondary-analysis: 873 with 781 matching	Opioid exposure categorized by Average Daily Dose: <20mg, 20-49mg, 50-99mg, 100-199mg, 200+mg. Logistic models adjusted for: duration, income, history of EtOH abuse, interacting prescription drugs, total number of different opioids dispensed, long-acting opioid used, number of physicians prescribing opioids, number of pharmacies dispensing opioids	Risk estimates reported as adjusted OR  Risk of opioid overdose death A. 1 (reference) B. 1.32 (0.94-1.84) C. 1.92 (1.30-2.85) D. 2.04 (1.28-3.24) E. 2.88 (1.79-4.63)  Secondary using 120-day exposure window risk of opioid overdose death A. 1 (reference) B. 0.93 (0.60-1.42) C. 1.31 (0.86-1.99) D. 1.47 (0.98-2.19) E. 2.24 (1.62-3.10)	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC	Good

## Appendix E3. Observational Studies of Long-term Opioid Use and Fractures

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Nested case control United Kingdom	Cohort: Patients with non-cancer pain with at least 1 opioid prescription between 1/1/90 and 12/31/08 in the General Practice Research Database Cases (n=21,739): First-time diagnosed fracture of the hip, humerus, or wrist during 1990-2008, age 18-80 years, >2 years of medical history before index date; excluding patients with cancer, dementia, metabolic bone disease, Cushing syndrome, hyperparathyroidism, long-term immobilization, or alcohol or drug abuse, fracture within 2 years, MVA within 90 days, osteoporosis diagnosis prior to index date Controls (n=85,326): Up to 4 controls without fracture selected for each case, matched on age, sex, index date, and general practice	A. Opioid nonuse B. Current cumulative opioid use 1 prescription C. 2-3 opioid prescriptions D. 4-5 opioid prescriptions E. 6-20 opioid prescriptions F. 21-50 opioid prescriptions G. 51-100 opioid prescriptions H. >100 opioid prescriptions  1. Opioid nonuse 2. Current use 3. Recent use 4. Past use	Mean age (years): 62 Female sex: 77% Race: NR Pain condition: NR Pain duration: NR Pain severity: NR Mean dose:NR Most commonly prescribed opioids: dihydrocodeine, codeine, propoxyphene, tramadol

## Appendix E3. Observational Studies of Long-term Opioid Use and Fractures

Author, year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Li, 2013	Used General Practice Research Database, in which drug exposures and diagnoses (including fracture) have been validated	Screened: NR Eligible: NR Enrolled: NR Analyzed: 21,739 fracture cases and 85,326 controls Number not analyzable: NR	Smoking, BMI, number of general practice visits, recorded years before index date, opioid use (new vs. prevalent), comorbidities, comedications, types of pain, recent/past opioid use (matched on age, sex, index date, and general practice)	Adjusted OR for risk of hip, humerus, or wrist fracture A. 1 (reference) B. 2.70 (95% CI 2.34-3.13) C. 1.90 (95% CI 1.67-2.17) D. 1.44 (95% CI 1.22-1.69) E. 1.17 (95% CI 1.08-1.27) F. 1.06 (95% CI 0.98-1.15) G. 1.06 (95% CI 0.96-1.16) H. 1.12 (95% CI 0.99-1.25)  1. 1 (reference) 2. 1.27 (95% CI 1.21-1.33) 3. 1.05 (95% CI 0.99-1.13) 4. 0.96 (95% CI 0.92-1.01)	None	Good

## Appendix E3. Observational Studies of Long-term Opioid Use and Fractures

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Saunders, 2010	KQ2a, b	Cohort, Group Health Cooperative United States	Age 60+, initiating opioids (no opioid prescriptions in prior 6 months) with 3+ prescriptions in 90 days and a diagnosis of non-cancer pain 2-3 weeks prior to the index prescription. Exclusions: Cancer, <270 days enrollment in health plan in the year prior to index.	Opioid dose per day (mg/day): A: Not currently using B: 1-<20 mg/day C: 20-<50 mg/day D: ≥50 mg/day E: Any use	Mean age (years): 73 Female sex: 66% Race: NR Depression diagnosis: 22% Substance abuse diagnosis: 3.8% Dementia diagnosis: 4.8% Prior fracture: 2.6% HRT/bisphosphonate use: 34% Rxrisk score, mean (SD): 4272 (2455) Charlson Index , mean (SD): 1.32 (2.0) Pain diagnosis at index visit 42% back pain, 4.8% neck pain, 25% osteoarthritis, 2.4% headache, 34% extremity pain, 5.3% abdominal pain/hernia, 0.6% menstrual/menopausal pain, 0.2% temporomandibular disorder pain Mean morphine equivalent daily dose (mg): (s.d.) 12.8 mg (17.0) Sedative hypnotic use: 60% Antidepressant use: 57% Opioid prescribed: Hydrocodone: 42% Oxycodone: 24% Codeine combination: 14% Long-acting morphine: 8.3%

Note: The references are located in Appendix C.

CI=confidence interval; HRT=hormone replacement therapy; ICD-9=International Classification of Diseases; KQ=key question; NR=not relevant; RxRisk= drug index for prescription drugs.

## Appendix E3. Observational Studies of Long-term Opioid Use and Fractures

Author, year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Saunders, 2010	Fractures initially identified by ICD-9 codes (800xx-804xx; 807xx-809xx; 810xx-829xx; 2000-2006, excluded vertebral fractures) and verified by medical record review; medication data from Group Health Cooperative automated pharmacy files (over 90% of prescriptions); covariates from automated health care data	Screened: ~500,000 Eligible, enrolled, and analyzed: 2,341 Loss to followup: Not reported Duration of followup (mean, person-months) (SD): 32.7 (21.3)	Age, sex, tobacco use, depression diagnosis, substance abuse diagnosis, dementia diagnosis, index pain diagnosis, chronic disease comorbidity adjustors, sedative-hypnotic use, antidepressant use, HRT/bisphosphonate use, and prior fractures.	Fracture rate: 5.0%/year Adjusted HRs for risk of fracture A: 1 (reference) B: 1.20 (95% CI 0.92, 1.56) C: 1.34 (95% CI 0.89, 2.01) D: 2.00 (95% CI 1.24, 3.24) E: 1.28 (95% CI 0.99, 1.64)	National Institute of Drug Abuse	Fair

## Appendix E4. Observational Studies of Long-term Opioid Use and Cardiovascular Outcomes

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Carman, 2011	KQ2a, b	Retrospective cohort United States	Claim submitted for dispensing of opioids or COX-2 inhibitors for $\geq 180$ days from July 2002 to December 2005, patients aged $\geq 18$ years; controls from general populations matched on age, sex, and cohort entry date Exclude: History of MI or revascularization, cancer	A. Opioids (n=148,657) B. Rofecoxib (n=44,236) C. Celecoxib (n=64,072) D. Valdecoxib (n=20,502) E. General population not using opioids or COX-2 inhibitors (n=148,657)  1. 0 to <1350 mg MED per 90 days 2. 1350 to <2700 mg MED per 90 days 3. 2700 to <8100 mg MED per 90 days 4. 8100 to <18,000 mg MED per 90 days 5. $\geq 18,000$ mg MED per 90 days	<b>A vs. B vs. C vs. D vs. E</b> Age 18-29 years: 4.7% vs. 1.2% vs. 0.8% vs. 1.2% vs. 4.7% Age 30-39 years: 16.3% vs. 5.4% vs. 4.1% vs. 5.3% vs. 16.3% Age 40-49 years: 33.9% vs. 20.7% vs. 17.6% vs. 20.1% vs. 33.9% Age 50-64 years: 36.7% vs. 56.0% vs. 56.3% vs. 56.5% vs. 36.7% Age $\geq 65$ years: 8.4% vs. 16.6% vs. 21.2% vs. 16.9% vs. 8.4% Female sex: 40.3% vs. 39.5% vs. 39.6% vs. 34.9% vs. 40.3% Diabetics: 11.7% vs. 10.2% vs. 12.4% vs. 11.1% vs. 4.1% Pain condition: NR Duration of pain: NR severity of pain: NR Opioids prescribed: NR

## Appendix E4. Observational Studies of Long-term Opioid Use and Cardiovascular Outcomes

Author, Year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Carman, 2011	All relevant claims in database during study period	Screened: NR Eligible, enrolled, analyzed: 426,124	Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, CV and other other comorbidities, and use of concomitant medications	<p>Adjusted incidence rate of MI, incidence rate ratio</p> <p>A: 5.93 (95% CI 5.58 to 6.30); IRR 2.66 (95% CI 2.30 to 3.08)</p> <p>B: 3.54 (95% CI 3.11 to 4.01); IRR 1.94 (95% CI 1.65 to 2.29)</p> <p>C: 3.53 (95% CI 3.15 to 3.94); IRR 1.79 (95% CI 1.53 to 2.10)</p> <p>D: 3.40 (95% CI 2.76 to 4.14); IRR 1.74 (95% CI 1.41 to 2.16)</p> <p>E: 1.58 (95% CI 1.40 to 1.78); IRR 1 (reference)</p> <p>Adjusted incidence rates of MI or revascularization, incidence rate ratio</p> <p>A. 11.91 (95% CI 11.40 to 12.43); IRR 2.38 (95% CI 2.15 to 2.63)</p> <p>B. 7.98 (95% CI 7.33 to 8.67); IRR 1.93 (95% CI 1.72 to 2.15)</p> <p>C. 7.94 (95% CI 7.36 to 8.54); IRR 1.81 (95% CI 1.62 to 2.01)</p> <p>D. 7.53 (95% CI 6.56 to 8.60); IRR 1.75 (95% CI 1.50 to 2.01)</p> <p>E. 3.38 (95% CI 3.12 to 3.67); IRR 1 (reference)</p> <p>Dosing</p> <p>Compared to a cumulative dose of 0 to 1350 mg MED over 90 days, the IRR for 1350 to &lt;2700 was 1.21 (95% CI 1.02 to 1.45), for 2700 to &lt;8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to &lt;18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for &gt;18,000 mg was 1.73 (95% CI 1.32 to 2.26)</p>	GlaxoSmithKline	Fair

## Appendix E4. Observational Studies of Long-term Opioid Use and Cardiovascular Outcomes

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Case-Control UK General Practice Research Database United Kingdom	Cases (n=11,693): Age 18-80 years, 2 years of medical history data before index (onset of MI symptoms) Controls: (n=44,897): Up to 4 controls matched on age, gender, index date, and practice site using risk-set sampling Excluded: History of cancer, ischemic heart disease, heart failure, stroke, congenital heart disorders, heart transplat, arrhythmias, treated hypertension, diabetes, ETOH/Drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index.	A. Non-use B. Current (0-30 days from index) C. Recent (31-365 days out) D. Past Use (366-730 days out)  Cumulative use (number of prescriptions): 1. 1-2 2. 3-10 3. 11-50 4. >50	Mean age (years): 61.8 vs. 61.6 Female sex: : 31.1% vs. 31.3% Current smoker: 38.6% vs. 23.3% Low BMI (<18.5): 1.2% vs. 1.2% Normal BMI: 25.8% vs. 28.9% Overweight: 31.7% vs. 30.2% Obese: 13.8% vs. 11.3% Arthritis: 25% vs. 24.2% Rheumatoid arthritis: 3.2% vs. 1.8% Fibromyalgia: 1.1% Duration or severity of pain: NR Codeine: 16% vs. 15% Dihydrocodeine: 9.6% vs. 8.1% Propoxyphene: 13% vs. 11%

Note: The references are located in Appendix C.

BMI=body mass index; CI=confidence interval; CV= cardiovascular; IRR=incidence rate ratio; KQ=key question; MI=myocardial infarction; NR=not relevant.

## Appendix E4. Observational Studies of Long-term Opioid Use and Cardiovascular Outcomes

Author, Year	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Li, 2013	Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI)	Screened: 1,700,000 Eligible: Not reported Enrolled: 11,693 cases and 44,897 controls Analyzed: 11,693 cases and 44,897 controls	Age, gender, smoking, body mass index, number of general practice visits, years of medical history, opioid new versus prevalent use, co-morbidities, concomitant medications, abdominal and pelvic pain and other pain	Risk of MI (adjusted OR) A. 1 (reference) B. 1.28 (95% CI 1.19–1.37) C. 1.17 (95% CI 1.10–1.24) D. 1.06 (95% CI 0.98–1.14)  1. 1.10 (95% CI 1.03–1.18) 2. 1.09 (95% CI 1.02–1.17) 3. 1.38 (95% CI 1.28–1.49) 4. 1.25 (95% CI 1.11–1.40)	None disclosed	Good

## Appendix E5. Observational Studies of Long-term Opioid Use and Endocrine Outcomes

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Deyo, 2013	KQ2a, b	Cross-sectional Integrated healthcare United States	Ambulatory males aged $\geq 18$ years with diagnoses associated with low back pain Exclude: patients with evidence of systemic disease or trauma	A. Patients prescribed medication for erectile dysfunction or testosterone replacement (n=909) B. Patients not prescribed medication for erectile dysfunction or testosterone replacement (n=10,418)	<b>A vs. B</b> Mean age (years): 55.7 vs. 48.0 Female sex: 0% Race: 89% White, 3% Black, 3% Asian/Pacific Islander, 1% American Indian, 3.9% other (among records with race/ethnicity data available, 59% of total sample) Sedative-hypnotic use: 24.4% vs. 15.6% Diagnosis of depression: 17.3% vs. 11.3%	Review of medical and pharmacy records

Note: The references are located in Appendix C.

KQ=key question; MED=morphine equivalent dose; NIH/NCRR=National Institutes of Health/National Center for Research.

## Appendix E5. Observational Studies of Long-term Opioid Use and Endocrine Outcomes

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Deyo, 2013	Screened: NR Eligible: 11,327 Enrolled: 11,327 Analyzed: 11,327	Age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensing, type of opioid (short- vs. long-acting), depression, and smoking status	No opioid use vs. short-term use vs. episodic use vs. long-term use Prescription for sildenafil, tadalafil, or vardenafil 6 months before or after index visit: 6.3% (294/4,655) vs. 6.9% (324/4,696) vs. 7.3% (12/164) vs. 11.3% (204/1,812); p<0.001 Testosterone replacement 6 months before or after index visit: 0.5% (25/2,655) vs. 0.6% (30/4,696) vs. 1.2% (2/164) vs. 2.4% (44/1,812); p<0.001 Testosterone replacement or erectile dysfunction treatment: 6.7% (312/4,655) vs. 7.4% (346/4,696) vs. 7.9% (13/164) vs. 13.1% (238/1,812); p<0.001; OR 1.5, 95% CI 1.1 to 1.9  Dosing Daily opioid dose of >120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95% CI 1.0 to 2.4)	NIH/NCRR	Fair

## Appendix E6. Observational Studies of Long-term Opioid Use and Motor Vehicle Accidents

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Sampling Strategy
Gomes, 2013	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid prescription (excluding methadone (2003-2011) at least 6 months of continuous eligibility for public drug coverage before their index date and at least 1 opioid prescription with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, had missing information about age or sex, received palliative care services in the 6 months before their index date, lived in a long-term care home at the index date, or had a prescription for a nonstudy opioid with a duration that overlapped the index date.	Cases: ED with an external cause of injury related to road trauma (codes V00 to V89 from ICD-10) (n=5,300 matched a control) Controls: (n=5300) A. 1-<20 mg/day B. 20-<50 mg/day C. 50-<100 mg/day D. 100-<200 mg/day E. ≥200 mg/day	<b>Cases vs. Controls</b> Mean age (years): 45.76 vs 45.75 Female sex: 48.6% Urban resident: 83.75% vs. 83.98 Social Assistance: 22% vs. 21% Disability support: 67.9% vs. 66.6% Duration of use (years): 7.09 vs. 6.84  <u>Charlson score</u> No hospitalization: 61.7% vs. 62.3% 0: 23.4% vs. 22.4% 1: 6.85% vs. 6.32% ≥2: 7.96% vs. 8.49%	Incidence density sampling Cases were matched to controls by sex, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past year, and disease risk index (within 0.2 SD). Cases with no matched controls were excluded from analyses.

Note: The references are located in Appendix C.

CI=confidence interval; ED=emergency department; ICD=International Classification of Diseases.

## Appendix E6. Observational Studies of Long-term Opioid Use and Motor Vehicle Accidents

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2013	Screened population: 549,878 Eligible Cases:5300 Eligible Controls: 43,736 Controls matched 1:1	Logistic models adjusted for: age, past (3 years) hospitalization for alcoholism, past (1 year) ED visit for alcoholism, duration of opioid treatment, medication use in past 180 days (ie, selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past 1 year.	Risk estimates reported as adjusted OR  Risk of motor vehicle crash A. 1 (reference) B. 1.09 (95% CI 0.97-1.21) C. 1.07 (95% CI 0.94-1.22) D. 1.08 (95% CI 0.93-1.24) E. 1.00 (95% CI 0.88-1.15)  Dosing Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs, and number of physician and emergency department visits was 1.21 (1.02 to 1.42) for 20 to 49 mg, 1.29 (1.06 to 1.57) for 50-99 mg, 1.42 (1.15 to 1.76) for 100 to 199 mg, and 1.23 (1.02 to 1.49) for >200 mg	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC.	Good

## Appendix E7. Trials of Different Methods for Initiating and Titrating Opioids

Author Year	Study design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Jamison, 1998	RCT 16 weeks	Single center Pain clinic United States	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensify >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment Exclude: Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic claudication, non- ambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen  A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR  In all groups, max 1000 mg/day of naproxen 16 weeks	Mean age (years): 43 Female sex: 57% Race: NR Indication: 39% failed back syndrome, 25% myofascial pain syndrome, 19% degenerative spine disease, 14% radiculopathy, 3% discogenic back pain Prior opioid use: NR Mean pain duration: 79 months	Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36
Salzman, 1999	RCT 10 days	Multicenter Rheumatology clinics and others United States	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids Exclude: Contraindication to opioid history of substance abuse, unable to discontinue nonstudy narcotic, or current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control	A: Sustained-release Oxycodone (titrated)  B: Immediate-release Oxycodone (titrated)  Titration comparison  Mean dose A: 104 mg/day  Mean dose B: 113 mg/day  10 days	Mean age (years): 56 Female sex: 54% Race: 87% White, 13% Hispanic Indication: Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration: NR	Screened: NR Eligible: NR Enrolled: 57 Analyzed: 57

Note: The references are located in Appendix C.

NR=not reported; RCT=randomized control trial; SF=short form.

## Appendix E7. Trials of Different Methods for Initiating and Titrating Opioids

Author Year	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Jamison, 1998	Pain Intensity: timing not specified, Comprehensive Pain Evaluation Questionnaire Functional status: baseline and at end of treatment (SF-36) Symptom checklist: baseline and at end of treatment (Symptom Checklist-90) Weekly activity record at baseline and once a month Medication diary weekly Overall helpfulness during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	A vs. B vs. C Average pain (means, 0-100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (means, 0-100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (means, 0-100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (means): 11.2 vs. 15.0 vs. 31.6 Depression (means): 10.8 vs. 16.4 vs. 26.9 Irritability (means): 17.7 vs. 20.5 vs. 33.7 Level of activity (means, 0-100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (means): 5.9 vs. 5.9 vs. 6.1	A vs. B Somnolence: 27% (8/30) vs. 37% (10/27) Nausea: 50% (15/30) vs. 33% (9/27) Vomiting: 20% (6/30) vs. 4% (1/27) Postural hypotension: 0% vs. 0% Constipation: 30% (9/30) vs. 37% (10/27) Pruritus: 30% (9/30) vs. 26% (7/27) Confusion: 3% (1/30) vs. 0% Dry mouth: 0% vs. 11% (3/27) Dizziness: 30% (9/30) vs. 22% (6/27) Nervousness: 0% vs. 7% (2/27) Asthenia: 7% (2/30) vs. 11% (3/27) Headache: 13% (4/30) vs. 26% (7/27) Withdrawal due to adverse events: 20% (6/30) vs. 7% (2/27)	Roxane Laboratories (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane	Fair
Salzman, 1999	Pain Intensity: daily diary, categorical scale (0-3, none-severe) Study Medication Use: daily diary, amount used Rescue Drug Use: daily diary, amount used Achievement of Stable Pain Control: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication Time to Stable Pain Control: Days	A vs. B Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) (p = 0.36) Time to stable pain control: 2.7 vs. 3.0 days (p = 0.90). Mean number of dose adjustments: 1.1 vs. 1.7 adjustments (p = 0.58)	A vs. B vs. C Withdrawal due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 130% (6/54) (p=0.008 for A or C vs. B) Withdrawal due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54) Any adverse event: 76% vs. 70% vs. 61% Dizziness: 7% vs. 7% vs. 7% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Constipation: 7% vs. 3% vs. 11% Diarrhea: 7% vs. 5% vs. 2% Vomiting: 18% vs. 12% vs. 7% Nausea: 54% vs. 42% vs. 33% Somnolence: 9% vs. 7% vs. 0% Pruritus: 4% vs. 2% vs. 7%	Purdue Pharma sponsored study 2 authors employees of Purdue Role not otherwise reported.	Fair

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Allan, 2005	RCT 13 months	Europe  Multicenter (number of sites not clear)	Adults with chronic low back pain requiring regular strong opioids Exclude: Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h)  B: Sustained-release morphine (titrated from 30 mg q 12 hrs) (Mean dose: 140 mg)	Avg. 54.0 years, 61% female Race: not reported, Prior opioid use not reported 35% nociceptive, 4% neuropathic, 46% nociceptive and neuropathic, 3% nociceptive with psychologic factors, 4% neuropathic with psychologic factors, 83% mechanical low back pain, 8% inflammatory 39% trauma/surgery, 1% metabolic, 3% other Pain duration average 124.7 months	Number approached and eligible not reported 683 randomized (338 to transdermal fentanyl and 342 to sustained-release morphine, 3 group assignment not reported)	Pain score (mean, 0-100 VAS) Severe pain at rest Severe pain on movement Severe pain during the day Severe pain at night Rescue strong opioids use Quality of life (SF-36) Loss of working days Withdrawal due to lack of efficacy

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Allan, 2005	<p>Transdermal fentanyl (A) vs. sustained-release morphine (B): Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B)</p> <p>Severe pain at rest (per protocol analyses, N=248 and 162): 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided)</p> <p>Severe pain on movement (per protocol): 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61</p> <p>Severe pain during the day (per protocol): 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385</p> <p>Severe pain at night (per protocol): 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided)</p> <p>Rescue strong opioids use: 154/296 (52%) (A) vs. 154/291 (53%) (B).</p> <p>Quality of life (SF-36): No differences between interventions</p> <p>Loss of working days: No differences between interventions</p> <p>Withdrawal due to lack of efficacy: 18/335 (5%) vs. 15/342 (4%)</p>	<p>Transdermal fentanyl (N=338) vs. sustained-release oral morphine (N=342)</p> <p>Any adverse event: 87% vs. 91%</p> <p>Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p&lt;0.05)</p> <p>Nausea: 54% vs. 50%</p> <p>Vomiting: 29% vs. 26%</p> <p>Somnolence: 17% vs. 30%</p> <p>Dizziness: 25% vs. 24%</p> <p>Fatigue: 17% vs. 14%</p> <p>Pruritus: 15% vs. 20%</p> <p>Application site reactions: 9% in transdermal fentanyl group. Deaths: None; Addiction: None reported. Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p&lt;0.001)</p> <p>Use of antiemetics/anticholinergics: 38% vs. 36%</p> <p>Use of antihistamines: 21% vs. 12% (p=0.002)</p> <p>Withdrawal (Overall): 52% (177/338) vs. 47% (162/342).</p> <p>Withdrawal (adverse events): 125/335 (37%) vs. 104/337 (31%) (p=0.098)</p>	<p>Janssen Pharma- ceutica</p> <p>One author employed by Janssen</p>	Fair

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Mitra, 2013	RCT 12 months	One site in Townsville, Australia	Inclusion: Patients > 18, reporting persistent pain for greater part of day and night for at least 1 year, opioid-naïve, appropriate for treatment with transdermal patches after medical assessment, with no comorbid psychiatric history.	A: TDB initial dose=5 mcg/h, n=22; B: TDF initial dose=12.5 mcg/h, n=24; Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	None reported by treatment group: Age, mean (range): 49 (22-80); Male: 48%; Back pain: 61%; Other types of pain: 39%; Duration of pain, mean (range): 11.7 yrs (6 mos to 50 yrs); Duration of follow-up: 3 mos (35%), 6 mos (13%), 12 mos (52%)	Considered for trial: 82; Enrolled: 46; Completed and analyzed at 12 mos: 30 (TDB-14 pts and TDF-16 pts)	SPAASMS: Activity & mobility: Rescue pain meds: GP/ED visits: Sleep quality: Side effects: Mood: Pain VAS: DASS21: PDI:

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Mitra, 2013	<p>12 month results: 16 of 46 patients continued for 12 mos and gained effective relief; SPAASMS: Score=13/28 possible in both groups at 12 mos (reading from Figure 5d) Activity &amp; mobility: no numbers provided, groups look similar at 12 mos; Rescue pain meds: initially higher in TDF group; higher in TDB group near study end (no numbers provided); GP/ED visits: increase in visit frequency in TDB group near study end (no numbers provided); Sleep quality: No significant difference between groups (no numbers provided) Side effects: see Adverse event column Mood: TDB had relatively better score at 12 mos (no numbers provided); Pain VAS: 3-point (scale 1-10) reduction in pain in 11% in each treatment group (raw numbers not reported); DASS21: TDB had relatively better score at 12 mos (no numbers provided); PDI: looks similar in Figure 5b (no numbers provided)</p>	<p>Discontinued due to AEs or unsatisfactory relief (not separated by AEs only): A: TDB: 8/22 (41%); number patients with side effects at 12 mos≤1 (reading from Figure 4a); number patients with local skin reaction at 12 mos=1 (reading from Figure 4b); B: TDF: 8/24 (37.5%) number patients with side effects at 12 mos≤1 (reading from Figure 4a); number patients with local skin reaction at 12 mos=0 (reading from Figure 4b)</p>	Private Practice Research Fund of Townsville	Poor

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Wild 2010	RCT 12 months	53 sites in North America; 36 sites in Europe	<p>Inclusion: Men/nonpregnant, nonlactating women ≥18 yrs, with diagnosis of moderate/severe knee or hip osteo, or LBP of noncancer origin; ≥ 3 mo history pain prior to screening, dissatisfied with current analgesic; NRS score ≥4 (of 11) at baseline, after 3-7 day washout from previous anagesics.</p> <p>Exclusion: lifelong seizures; mild/moderate TBI, stroke, TIA, brain neoplasm within one year; severe TBI within 15 years; malignancy within 2 years; history of etoh/drug abuse; history of Hep B/C; HIV; allergy to oxycodone/acetaminophen; participation in previous tapentadol studies; patients with reference joint or back surgery within 3 months or during study; hepatic or renal dysfunction, uncontrolled hypertension, significant pain with conditions other than osteo or LBP.</p>	<p>A. Tapentadol ER 100-250 mg BID (adjustable) (n=894; 413 completed 6 mos; 227 completed 12 mos)</p> <p>B. Oxycodone CR 20-50 mg BID (adjustable) (n=223; 78 completed 6 mos; 44 completed 12 mos)</p>	<p>A vs B Age, mean (SD): 56.8 (12.5) vs 58.1 (11.8); Age category: &lt;65 vs 70%; Male: 42.4% vs 43.9%; Race: White:88.6% vs 91.0%, Black: 6.7% vs 5.8%, Hispanic: 2.9% vs 1.8%, Other: 1.8% vs 1.3%; BMI: 31.7 vs 31.8; Pain intensity, Mean (SD): 7.6 (1.5) vs 7.6 (1.62); Pain intensity category: Moderate: 10% vs 13%, Severe: 90% vs 87%; Prior opioids: No 47.1% vs 49.8%</p>	<p>Screened: 1123 Randomized: 1121 Received drug: 1117 Discontinued-A: 53.8%; 22.7% to AEs; Discontinued-B: 65.0; 36% to AEs%</p>	<p>AEs; vital signs; physical exams; labs; ECGs; PROs: PAC-SYM; COWS; SOWS; TEAEs</p>

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Wild 2010	<p>Mean (SE) pain intensity score: decreased 4.4 (0.09) vs 4.5 (0.17);</p> <p>Global assessment, score of (very) much improved: 48.1% (394/819) vs 41.2% (73/177);</p> <p>Median duration of treatment (days):</p> <p>A: 268 (range 1-385)</p> <p>B: 59 (range 1-384);</p> <p>Mean (SD) total daily dose for study completers:</p> <p>A: 380.5 (102.43) mg</p> <p>B: 71.0 (22.89) mg</p> <p>Concomitant nonopioid analgesics (NSAIDs, ASA, acetaminophen):</p> <p>A: 19.9% (178/894)</p> <p>B: 17% (38/223)</p>	<p>Discontinued due to AEs:</p> <p>A: 22.7%</p> <p>B: 36.8%;</p> <p>At least one TEAC:</p> <p>A: 85.7% (766/894)</p> <p>B: 90.6% (202/223);</p> <p>A vs B:</p> <p>Constipation: 22.6% vs 38.6%;</p> <p>Nausea: 18.1% vs 33.2%</p> <p>Vomiting: 7.0% vs 13.5%;</p> <p>Pruritis: 5.4% vs 10.3%;</p> <p>Dizziness: 14.8% vs 19.3%;</p> <p>Serious TEACs: 5.5% vs 4.0%;</p> <p>No relevant AEs on labs, vitals, ECGs;</p> <p>No deaths;</p> <p>Mean change (SE) PAC-SYM: 0.3 (0.05) vs 0.5 (0.14);</p> <p>COWS, 5 days post treatment, no withdrawal: 88% (145/166) vs 84% (42/50);</p> <p>Mean SOWS at 2-5 days post treatment - consistent with COWS</p>	J & J; grunenthal GmbH	Fair

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
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Note: The references are located in Appendix C.

AE=adverse event; ASA=aspirin; ECG=electrocardiogram; BID=twice daily; COWS=Clinical opiate withdrawal scale; DASS2= Depression Anxiety Stress Scale; GmbH=German liability company; GP/ED=general practitioner/emergency department; Hep B/C=Hepatitis B and/or C; HIV=human immunodeficiency virus; LBP=low blood pressure; NSAIDS=non-steroidal anti-inflammatory drug; PDI=physical disability index; ITT=intent to treat; PROs=patient reported outcomes; PAC-SYM=patient assessment of constipation syndrome; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SOWS=Subjective Opiate Withdrawal Scale; SPAASMS= score, physical, activity level, additional pain medication, additional physician/ER visits, sleep quality, mood, medication side-effects; TBI=traumatic brain injury; TDB=transdermal buprenorphine; TDF=transdermal fentanyl; VAS=visual analog scale; TEAC=treatment emergent adverse criteria; TEAEs=Treatment-Emergent Adverse Event; TIA=transient ischemic attack.

## Appendix E8a. Head-to-Head Trials of Different Long-acting Opioids

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
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## Appendix E8b. Observational Studies of Different Long-acting Opioids

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Hartung, 2007	Retrospective cohort Medicaid claims United States	Patients prescribed at least one $\geq$ 28-day supply of methadone, ER oxycodone, ER morphine, or transdermal fentanyl	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C vs. D Mean age: 70.6 vs. 51.1 vs. 57.4 vs. 58.5 years Female sex: 74% vs. 63% vs. 65% vs. 65% Race: 6.1% vs. 10.5% vs. 7.7% vs. 9.6% non-White Mean MED dose: 96 vs. 247 vs. 67 vs. 74 mg Cancer: 19.9% vs. 18.3% vs. 25.2% vs. 26.1% Osteoarthritis: 13.7% vs. 22.6% vs. 19.3% vs. 18.0% Back pain: 17.5% vs. 41.8% vs. 35.0% vs. 27.3%	Review of claims using ICD-9 codes

## Appendix E8b. Observational Studies of Different Long-acting Opioids

Author, Year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Hartung, 2007	Screened: NR Eligible: NR Enrolled: 5,684 Analyzed: 5,684	Age, sex, race, long-term care residence, number of unique prescribers, disease severity, concomitant prescriptions known to interact with opioids, type of presumed pain diagnosis, history of abuse or dependence, enrollment in a substance abuse treatment program	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI 0.46 to 1.08) vs. HR 0.71 (95% CI 0.54 to 0.94) vs. 0.80 (95% CI 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI 0.46 to 1.08) or overdose symptoms	NR	Fair

## Appendix E8b. Observational Studies of Different Long-acting Opioids

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Krebs, 2011	Retrospective cohort VA United States	New prescription for $\geq 28$ days' supply of PO methadone or LA morphine tabs/caps from a VA outpatient pharmacy between 1/1/2000 and 12/31/2007. Preceded by 30 day window free of LA opioid prescriptions.  Excluded: Liquid/IV forms of methadone/morphine; metastatic cancer, palliative care, receiving methadone for addiction; methadone 40 mg diskettes; $< 17$ or $> 100$ years of age; missing gender data.	A: Methadone (n=28,554) B: Long-acting morphine sulfate (MS) (n=79,938)	Mean (SD) daily LA MS dose: 67.5 mg (77.4); median (IQR) 46.7 (45); Mean (SD) daily methadone dose: 25.4 mg (25.8); median (IQR): 20 (20); 99th %ile MS: 360-7200 mg; 99th %ile methadone: 124-560 mg; A vs B: Age: mean (SD): 56 (12) vs 59 (13); Race: white: 40% vs 41%; nonwhite: 52% vs 49%; unknown: 8% vs 9%; MI: 9% vs 11%; CHF: 15% vs 19%; PVD: 17% vs 20%; CVD: 15% vs 17%; COPD: 35% vs 38%; Diabetes: 31% vs 33%; Malignancy: 15% vs 26%; Depression: 62% vs 54%; Bipolar: 10% vs 8%; Anxiety: 32% vs 27%; EtOH: 25% vs 22%; Drug disorderz; 25% vs 18%; Tobacco: 47% vs 42% Back pain: 85% vs 76%; Joint/limb pain: 86% vs 82%; Headache: 25% vs 21%; Neuropathic pain: 35% vs 29%	All patients meeting eligibility criteria

Note: The references are located in Appendix C.

CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; LA=long acting; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease SD=standard deviation; VA=Veterans Affairs; VISN=Veterans integrated service networks.

## Appendix E8b. Observational Studies of Different Long-acting Opioids

Author, Year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Krebs, 2011	Screened: Not applicable; Eligible: 133,969; Enrolled: 108,492; Analyzed: 98,068; Loss to followup: 3,347 (died); 94,721 (censored)	Propensity score for receiving methadone was estimated with logistic regression model that included age, gender, race, geographic area (VISN), depression, anxiety, bipolar dx, schizophrenia, etoh, drug, tobacco disorders, back pain, joint/limb pain, headache, neuropathic pain; Medical comorbidities included via Romano adaptation of Charlson Comorbidity Score; Quintiles calculated and then used in Cox model; Interaction term consisting of propensity quintile and opioid group	All-cause mortality: Unadjusted: 3,347 (3.4%) patients died; highest mortality within 1st 30 days (1.2% in methadone and 3.7% in MS); raw death rates form MS higher than methadone for all 30- day intervals; Death rate: Quintile #1 (0.042 vs 0.133); Quintile #2 (0.034 vs 0.078); Quintile #3 (0.025 vs 0.053); Quintile #4 (0.022 vs 0.034); Quintile #5 (0.017 vs 0.020); Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62) Quintile #1: 0.36 (95% CI: 0.26, 0.49); Quintile #2: 0.46 (0.37, 0.56); Quintile #3: 0.50 (0.41, 0.61); Quintile #4: 0.66 (0.54, 0.81); Quintile #5: 0.92 (0.74, 1.16); Results robust in validation dataset	VA	Fair

## Appendix E9. Trials of Opioid Dose Escalation Versus Dose Maintenance or Use of Maximum Dose Ceilings

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Outcomes Assessed
Naliboff 2011	RCT 12 months	VA pain clinic U.S.	Patients referred to chronic pain clinic; nonmalignant chronic pain for at least 6 months; clinician determination that patient was eligible for long-term opioids.  Excluded: anticipated surgery, post-op pain, pulmonary disease or CHF, current or history of substance abuse disorder, hospitalization for psych disorder in past 2 years	A. Escalating opioid dose; mean morphine equivalent 52 mg (n=67)  B. Stable opioid dose; mean morphine equivalent 40 mg (n=73)	A vs B Mean age 53 vs 52 years 89% vs 99% male Race not reported Pain: -78% vs 77% musculoskeletal -19% vs 19% neuropathic -3% vs 4% complex Initial morphine equivalent 29.2 (SD 19.6) vs 32.3 (SD 23.1) mg Mean usual VAS 7.0 (SD 1.9) vs 6.7 (SD 1.8) Mean worst VAS 8.4 (SD 1.2) vs 8.0 (SD 1.7) Mean ABC score 1.5 (SD 2.0) vs 1.6 (SD 2.1) Mean ODI 48.6 (SD 12.6) vs 47.8 (SD 14.0)	Screened: not reported Eligible: 140 Enrolled: 140 Analyzed: 134 Loss to followup: 10/140 (7%)	Pain Functional disability Use of nonopioid medications

Note: The references are located in Appendix C.

CI=confidence interval, NSAID=nonsteroidal anti-inflammatory drug, ODI=Oswestry Disability Index, RCT=randomized controlled trial, SD=standard deviation, US=United States, VA=Veterans Affairs, VAS=Visual Analog Scale.

## Appendix E9. Trials of Opioid Dose Escalation Versus Dose Maintenance or Use of Maximum Dose Ceilings

Author Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Naliboff 2011	<p>A vs B</p> <p>Mean VAS usual pain at 12 months: 5.6 (SD 1.5) vs 6.2 (SD 1.5); p=0.11*</p> <p>Usual pain VAS decrease <math>\geq 1.5</math> points: 19/67 (28%) vs 15/73 (20%); RR 1.38; 95% CI 0.76 to 2.49</p> <p>Mean VAS pain relief at 12 months: 6.0 (SD 1.7) vs 5.3 (SD 1.8); p=0.11*</p> <p>Increase in pain relief <math>\geq 1.5</math> points: 19/67 (29%) vs 11/73 (15%); RR 1.88; 95% CI 0.97 to 3.66</p> <p>Worst pain VAS decrease <math>\geq 1.5</math> points: 9/67 (14%) vs 4/73 (6%); RR 2.45; 95% CI 0.79 to 7.59</p> <p>Mean ODI at 12 months: 45.8 (SD 14.8) vs 45.0 (SD 19.4); p=0.85*</p> <p>ODI decrease <math>\geq 10</math> points: 19/67 (29%) vs 20/73 (23%); RR 1.04; 95% CI 0.61 to 1.76</p> <p>Use of nonopioid treatments (A: n=64; B: n=70):</p> <ul style="list-style-type: none"> <li>-NSAID: 35/64 (55%) vs 42/70 (60%); RR 0.92; 95% CI 0.68 to 1.22</li> <li>-Muscle relaxant: 10/64 (15%) vs 14/70 (20%); RR 0.78; 95% CI 0.37 to 1.63</li> <li>-Anti-seizure: 40/64 (63%) vs 46/70 (66%); RR 0.95; 95% CI 0.74 to 1.23</li> <li>-Anti-anxiety: 19/64 (29%) vs 24/70 (34%); RR 0.87; 95% CI 0.53 to 1.42</li> <li>-Antidepressants: 45/64 (71%) vs 48/70 (69%); 1.03; 95% CI 0.82 to 1.28</li> <li>-Topical: 11/64 (17%) vs 11/70 (16%); RR 1.06; 95% CI 0.49 to 2.28</li> <li>-Injectable: 17/64 (26%) vs 25/70 (36%); RR 0.74; 95% CI 0.44 to 1.24</li> <li>-Physical therapy: 31/64 (48%) vs 44/70 (63%); RR 0.77; 95% CI 0.57 to 1.05</li> </ul> <p><i>*p-value calculated based on completers (A: n=34; B: n=32)</i></p>	<p>A vs B</p> <p>All-cause withdrawals: 33/67 (49%) vs 41/73 (56%); RR 0.88; 95% CI 0.64 to 1.20</p> <p>Withdrawal due to opioid misuse: 16/67 (24%) vs 22/73 (30%); RR 0.79; 95% CI 0.46 to 1.38</p>	Department of Veterans Affairs	Fair

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ashburn, 2011	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	46 centers United States	Patients aged 18 to 80 years with $\geq 3$ months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving $\geq 60$ mg/day MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome
Davies, 2011	RCT (crossover) 3-21 days	35 cancer centers Europe and India	Patients with histologically confirmed cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent $\geq 60$ mg MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl pectin nasal spray (n=106 for safety and n=84 for efficacy) B. Immediate-release morphine sulfate (n=106 for safety and n=84 for efficacy)	Mean age: 55.9 years Female sex: NR Race: NR

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Ashburn, 2011	Screened: 486 Eligible: 360 Enrolled: 323 (titration phase) Analyzed: 320 (safety), 183 (efficacy)	Pain intensity, pain relief, and total pain relief	A vs. B Pain intensity difference at 15 minutes: 0.82 vs. 0.60 (p<0.001) Pain relief at 15 minutes: 0.69 vs. 0.53 (p<0.05) Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes (p<0.05)	A vs. B Any adverse event: 38% (106/281) vs. 31% (88/284); RR 1.22 (95% CI 0.97 to 1.53)	Cephalon, Inc.	Good
Davies, 2011	Screened: NR Eligible: NR Enrolled: 110 (titration phase) Analyzed: 106 (safety population), 84 (randomized after titration phase)	Pain intensity, pain relief, and total pain relief	A vs. B ≥2-point reduction in pain intensity at 10 minutes: 52.4% vs. 45.4% (p<0.05) ≥2 pain relief at 15 minutes: 60.2% vs. 53.4% (p<0.05) Total pain relief ≥33% at 15 minutes: 52.3% vs. 43.5% (p<0.01)	A vs. B Treatment-emergent adverse events resulting in discontinuation: 6 vs. 2	No financial support provided	Fair

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Portenoy, 2007	RCT 3 weeks	Multicenter Clinic setting not described United States	18 to 80 years, chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis resulting in functional disability for at least 3 months, receiving morphing average pain intensity scale in 24 hours prior to entry, duration of breakthrough pain less than 4 hours, use of an opioid to treat breakthrough pain described as at least somewhat effective Exclude: Uncontrolled or rapidly escalating pain, allergies or contraindications to study drug, cardiopulmonary disease that might affect safety, psychiatric or medical disease that might affect data collection, alcohol or substance abuse during the past 5 years, lactating, participated in an earlier fentanyl buccal tablet trial, or expected to have surgery during study	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	Not reported for randomization groups Mean age: 47 years Female gender: 55% Non-white race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Portenoy, 2007	Screened: 124 Eligible: NR Enrolled: 105 (in open-label dose titration), 77 (in randomized phase; randomized to one of 3 treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets in different orders)	Pain intensity: 0 to 10 scale Pain relief: 5-point scale (0 = none to 4 = complete) Onset time of "meaningful" pain relief	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 70% (289/413) vs. 30% (63/207) ( $p < 0.0001$ ) Proportion of breakthrough pain episodes with $\geq 33\%$ reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) ( $p \leq 0.0001$ ) Proportion of breakthrough pain episodes with $\geq 50\%$ reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) ( $p \leq 0.0001$ ) Proportion of breakthrough pain episodes with $\geq 33\%$ reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) ( $p \leq 0.0001$ ) Proportion of breakthrough pain episodes with $\geq 50\%$ reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) ( $p \leq 0.0001$ )	All data reported only for buccal fentanyl Withdrawn due to adverse event: 1% (1/77) Serious adverse events: 3% (2/77) Nausea: 1% Dizziness: 4% Somnolence: 0% Dysgeusia: 8% Vomiting: 0% Dry mouth: 4%	Cephalon, Inc.	Good

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Simpson, 2007	RCT (crossover) 3 weeks	Multicenter Clinic setting not described United States	18 to 80 years old, $\geq 3$ months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity $< 7$ on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain, use of opioid therapy for breakthrough pain described as at least partially effective; had to identify effective dose during dose-titration phase to be entered into randomized portion of trial Exclude: Unstable, uncontrolled, or rapidly escalating pain; allergies or other contraindications to study drug; alcohol or substance abuse in past 5 years; significant cardiopulmonary disease; significant medical or psychiatric disease; pregnancy or lactating	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain  B: Placebo  Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	NR for randomization groups
Webster, 2013	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	42 sites Setting not described United States	Patients aged 18 to 80 years with $> 3$ months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving $> 60$ mg/day MED, with and average pain intensity $\leq 6$ and 1-4 episodes of breakthrough pain per day Exclude: recent history of substance abuse, positive UDT	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	Mean age: 50.8 years Female sex: 58% Race: 91% White, 7% Black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1

## Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Simpson, 2007	Screened: 129 Eligible: NR Enrolled: 103 (in open-label dose titration), 79 (in randomized phase; randomized to one of 3 crossover treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets)  Discontinued early: 2.5% (2/79)	Pain Intensity: 0 to 10 scale Sum of Pain Intensity differences from 5 through 60 minutes after administration of study drug	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with $\geq$ 50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p $\leq$ 0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR=0.28, 95% CI 0.18 to 0.42)	All data reported only for buccal fentanyl: Withdrawn due to adverse event: 2.5% (2/79); 12% (12/103) withdrawn due to adverse events during open-label dose titration Nausea: 0% Dizziness: 1% Somnolence: 1% Vomiting: 0% Application site adverse event: 8% (8/103) during open-label dose titration	Cephalon, Inc.	Good
Webster, 2013	Screened: 307 Eligible: NR Enrolled: 213 (titration phase) Analyzed: 211 (safety), 137 (efficacy)	Pain intensity, pain relief, and total pain relief	A vs. B Pain intensity difference at 15 minutes: 0.88 vs. 0.76 (p<0.001) Pain relief at 15 minutes: 38% vs. 34% (p<0.05) Meaningful pain relief within 15 minutes: 17% vs. 16% (p=NS) Meaningful pain relief within 30 minutes: 46% vs. 38% (p<0.01)	A vs. B Any adverse event: 18% (25/138) vs. 14% (20/142); RR 1.29 (95% CI 0.75 to 2.20)	Teva Pharmaceuticals (formerly Cephalon, Inc.)	Good

# Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
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Note: The references are located in Appendix C.  
CI=confidence interval; MED=morphine equivalent dose; NR=not relevant ; RCT=randomized controlled trial.

# Appendix E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
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# Appendix E11. Trials of Decreasing Opioid Doses or of Tapering Off Opioids Versus Continuation of Opioids

Author year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Cowan, 2005	RCT (crossover) 60 hours	Single center Pain clinic United Kingdom	>18 years, chronic noncancer pain on sustained-release oral morphine for $\geq 30$ days, willing to abstain from morphine, able to give regular blood samples Exclude: Pain not adequately controlled by immobilization and alternative medication, patient may require a sudden change in opioid dose, pregnant or lactating	A: Continued sustained-release morphine for 60 hours B: Abrupt cessation of morphine for 60 hours	Mean age: 56 years Female gender: 40% Non-white race: Not reported Pain >5 years: 90% Duration of morphine use: mean 2.2 years Dose $\leq 60$ mg/day: 90%	Screened: 33 Eligible: 11 Enrolled: 10 Analyzed: 10

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Note: The references are located in Appendix C.  
RCT=randomized controlled trial.

## Appendix E11. Trials of Decreasing Opioid Doses or of Tapering Off Opioids Versus Continuation of Opioids

Author year	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Cowan, 2005	Effects of cessation of opioids: Unvalidated 19-item questionnaire Brief Pain Inventory Evaluation of physiologic parameters (heart rate, blood pressure, temperature, respiration, pupil size)	Continued sustained-release morphine vs. abrupt cessation Brief Pain Inventory, average pain in last 24 hours (0 to 10): 3.2 vs. 5.3 ( $p < 0.026$ ) Pain interference with general activity in last 24 hours (0 to 10): 0.2 vs. 4.3 ( $p < 0.027$ ) Physiologic parameters: No differences	Adverse events during cessation of opioids: 3/10 (30%) "Do you have any drug craving?": 0/10 after abrupt cessation of therapy	Janssen-Cilag Ltd., Napp Pharmaceuticals	Poor

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## Appendix E12. Nonrandomized Trials of Different Opioid Tapering Protocols and Strategies

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ralphps, 1994	Non-randomized trial 6 months	Inpatient, single center United Kingdom	Patients referred to inpatient pain management, on opioids, chronic non-cancer pain, with any two of following: widespread disruption in activity due to pain, habitual over-activity leading to increased pain, regular use of analgesics and/or sedatives for >6 months, high affective distress, use of unnecessary aids, high levels of reported or observed pain behaviors, work reduced, impaired, or ceased owing to pain Exclude: Cannot use English, cannot climb stairs, current major psychiatric illness, unavailable for 4-week program, suitable for further physical treatments after medical examinations, pain of less than 1 year's duration, under 18 years old, currently using opioids for treatment of drug dependency	A: Patient-controlled reduction (patient discussed desired rate of reduction, aiming for abstinence by discharge, allowed to take longer if they wished, patients kept pills in room, plans adjusted as appropriate)  B: Cocktail method (opioid mixed into a cocktail with dose gradually reduced, patient unaware of reduction schedule)	Mean age: 47 vs. 50 years Female gender: 49% vs. 71% Non-white race: Not reported Pain duration: 124 vs. 101 months Pain distress (0 to 100): 66 vs. 73 Mean opiate dose: 35.8 mg/day
Tennant, 1982	Non-randomized clinical trial 3 to 18 months	Single center Outpatient clinic United States	Patients on opioids who volunteered for outpatient treatment for withdrawing opioids	A: Detoxification/ counseling: Detoxification over 3 weeks with methadone, propoxyphene, clonidine, diphenoxylate, or sedative-hypnotics, followed by weekly psychotherapeutic counseling  B: Detoxification/ maintenance: Detoxification as above, with maintenance on opioid if detoxification unsuccessful	Mean age: 33 vs. 44 years Female gender: 48% vs. 52% Nonwhite race: 19% vs. 14% Duration of opioid use: 7.2 vs. 9.2 years Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%

Note: The references are located in Appendix C.  
NR=not reported.

## Appendix E12. Nonrandomized Trials of Different Opioid Tapering Protocols and Strategies

Author Year	Screened Eligible Enrolled Analyzed	Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Ralps, 1994	Screened: 132 Eligible: NR Enrolled: 108 (63 to patient-controlled method and 45 to cocktail method) Analyzed: 108  Attrition: 24% (26/108)		Abstinent at discharge Abstinent at 6 month after discharge Use of other drugs, pain, or psychological variables at 6 months	Patient-controlled reduction versus cocktail method Abstinent at discharge: 68% vs. 89% (p<0.05) Abstinent 6 months after discharge: 54% (27/50) vs. 56% (18/32) Use of other drugs, pain, or psychological variables at 6 months: No differences between groups	NR	King Edwards Hospital Fund for London, Special Trustees of St. Thomas Hospital, and the South East Thames Regional Health Authority	Poor
Tennant, 1982	Screened: NR Eligible: NR Enrolled: 42 (21 to detoxification/ counseling and 21 to detoxification/ maintenance) Analyzed: 42		Proportion remaining in treatment past 3 weeks Proportion abstinent from opioids (as judged by history, negative urine test, and no further requests for opioids)	Detoxification/counseling vs. detoxification/maintenance Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	NR	NR	Poor

## Appendix E13. Prospective Studies on Use of Screening Instruments to Predict the Risk of Aberrant Drug-related Behaviors

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Akbik 2006	Prospective cohort	Chronic pain patients attending one of two pain clinics	Mean age 43 years (SD 9.6) 33% female 86% White, other races not reported Pain: 39% back	n=155 (with reference standard, of 397 enrolled)	SOAPP	Self-report	Positive urine screening	SOAPP score ≥8: 30
Jones 2012 (Study 2)	Retrospective cohort	Consecutive pain clinic patients being evaluated for risk of opioid addiction prior to opioid initiation	Mean age 48 years (SD 13) 56% female 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia, 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	n=263	ORT PMQ SOAPP-R Clinician assessment	Self-report; clinician interview	Subsequent opioid discontinuation due to abuse	ORT score >4: 8 PMQ score >30: 13 SOAPP-R score >17: 20 Clinician assessment of high-risk: 27
Moore 2009	Retrospective cohort	New adult patients at a pain clinic	Mean age 44 years (SD 11) 60% female Race not reported Pain not reported	n=48	SOAPP DIRE ORT Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Subsequent opioid discontinuation due to abuse	SOAPP: 35 DIRE: 8 ORT: 21 Clinical interview: 37

## Appendix E13. Prospective Studies on Use of Screening Instruments to Predict the Risk of Aberrant Drug-related Behaviors

Author, Year	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Akbik 2006	SOAPP score ≥8: 59	SOAPP score ≥8: 37	SOAPP score ≥8: 14	SOAPP score ≥8: 0.68 (95% CI 0.52 to 0.81)	SOAPP score ≥8: 0.39 (95% CI 0.29 to 0.49)	SOAPP score ≥8: 1.11 (95% CI 0.86 to 1.43)	SOAPP score ≥8: 0.83 (95% CI 0.52 to 1.31)	Not reported	Fair
Jones 2012 (Study 2)	ORT score >4: 19 PMQ score >30: 41 SOAPP-R score >17: 65 Clinician assessment of high-risk: 57	ORT score >4: 142 PMQ score >30: 134 SOAPP-R score >17: 65 Clinician assessment of high-risk: 84	ORT score >4: 33 PMQ score >30: 25 SOAPP-R score >17: 11 Clinician assessment of high-risk: 11	ORT score >4: 0.20 (95% CI 0.15 to 0.27) PMQ score >30: 0.34 (95% CI 0.20 to 0.51) SOAPP-R score >17: 0.39 (95% CI 0.26 to 0.54) Clinician assessment of high-risk: 0.71 (95% CI 0.54 to 0.84)	ORT score >4: 0.88 (95% CI 0.82 to 0.93) PMQ score >30: 0.77 (95% CI 0.69 to 0.80) SOAPP-R score >17: 0.69 (95% CI 0.63 to 0.75) Clinician assessment of high-risk: 0.60 (95% CI 0.51 to 0.68)	ORT score >4: 1.65 (95% CI 0.78 to 3.51) PMQ score >30: 1.46 (95% CI 0.87 to 2.45) SOAPP-R score >17: 1.27 (95% CI 0.86 to 1.90) Clinician assessment of high-risk: 1.76 (95% CI 1.32 to 2.34)	ORT score >4: 0.91 (95% CI 0.78 to 1.06) PMQ score >30: 0.86 (95% CI 0.68 to 1.08) SOAPP-R score >17: 0.88 (95% CI 0.70 to 1.10) Clinician assessment of high-risk: 0.49 (95% CI 0.29 to 0.81)	ORT 0.53 PMQ 0.57 SOAPP-R 0.54	Poor
Moore 2009	Not calculable	Not calculable	SOAPP: 13 DIRE: 40 ORT: 27 Clinical interview: 11	SOAPP score ≥6: 0.73 DIRE score <14: 0.17 ORT score >4: 0.45 Clinical interview assessment medium or high risk: 0.77	Not reported	Not reported	Not reported	Not reported	Poor

## Appendix E13. Prospective Studies on Use of Screening Instruments to Predict the Risk of Aberrant Drug-related Behaviors

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Webster 2005	Prospective cohort	New chronic pain patients at a pain clinic	Mean age 44 years (SD 13) 58% female Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	n=185	ORT	Self-report	Documentation of aberrant behavior during followup	ORT score 1-3 (low risk): 1 ORT score 4-7 (moderate risk): 35 ORT score ≥8 (high risk): 40

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Note: The references are located in Appendix C.

AUROC=area under receiver operating characteristic curve; CI=confidence interval; DIRE= Diagnosis, Intractability, Risk and Efficacy Inventory; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SOAPP-R= Revised Screener and Opioid Assessment for Patients with Pain.

## Appendix E13. Prospective Studies on Use of Screening Instruments to Predict the Risk of Aberrant Drug-related Behaviors

Author, Year	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Webster 2005	ORT score 1-3 (low risk): 17 ORT score 4-7 (moderate risk): 88 ORT score high (≥8): 4	ORT score 1-3 (low risk): 92 ORT score 4-7 (moderate risk): 21 ORT score high (≥8): 105	ORT score 1-3 (low risk): 75 ORT score 4-7 (moderate risk): 41 ORT score high (≥8): 36	ORT score ≥4: 0.99 (95% CI 0.92 to 0.999)	ORT score ≥4: 0.16 (95% CI 0.10 to 0.24)	ORT score ≥4: 1.17 (95% CI 1.07 to 1.27) ORT score 1-3 (low risk): 0.08 (95% CI 0.01 to 0.62) ORT score 4-7 (moderate risk): 0.57 (95% CI 0.44 to 0.74) ORT score ≥8 (high risk): 14.34 (95% CI 5.35 to 38)	ORT score ≥4: 0.08 (95% CI 0.01 to 0.65)	Not reported	Fair

## Appendix F1. Quality Assessment of Cross-sectional Studies

Author, Year	KQ	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were outcome assessors blinded to patient characteristics?	Did the article report attrition?	Is there overall high loss to followup?	Were prespecified outcomes assessed in all patients?	Quality
Banta-Green, 2009	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Boscarino, 2010	KQ2a abuse	Yes; random	No	NA	NA	No (high proportion of nonrespondents)	Fair
Carrington Reid, 2002	KQ2a abuse	Yes	No	NA	NA	Yes	Fair
Compton, 2008	KQ2a abuse	Yes; consecutive	No	No	Unclear	Yes	Fair
Cowan, 2003	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Deyo, 2013	KQ2a , b endocrine	Yes	Unclear	NA	NA	Yes	Fair
Fleming, 2007 See also: Saffier, 2007	KQ2a abuse	Yes; all	No	NA	NA	Yes	Fair
Hojsted, 2010	KQ2a abuse	Unclear	No	NA	NA	Yes	Fair
Portenoy, 2007	KQ2a abuse	No (28% of eligible patients enrolled, not clear why most did not enroll)	No	Yes	Yes (Table 3)	Yes	Fair
Schneider, 2010	KQ2a abuse	Yes	No	NA	NA	No; UDT only in 82% of patients	Fair
Wasan, 2009	KQ2a abuse	Unclear	Yes	NA	NA	No	Fair

Note: The references are located in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question; NA=not applicable; UDT=urine drug test.

## Appendix F2. Quality Assessment of Cohort Studies

Author, Year	KQ	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there important differential loss to followup or overall high loss to followup?	Did the study perform appropriate statistical analyses on potential confounders?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality
Carman, 2011	KQ2a, b myocardial infarction	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Dunn, 2010	KQ2a, b overdose	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Hartung, 2007	KQ3c	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Krebs, 2011	KQ3c	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Fair
Saunders, 2010	KQ2a, b fractures	Yes	Unclear	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair

Note: The references are available in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question.

## Appendix F3. Quality Assessment of Case Control Studies

Author, Year	KQ	Did the study attempt to enroll all or random sample of cases using predefined criteria?	Were the controls derived from the same population as the cases?	Were the groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did the study use accurate methods for identifying outcomes?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Quality
Gomes, 2011	KQ2b overdose	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Gomes, 2013	KQ2b, motor vehicle accident	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013a	KQ2a fractures	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013b	KQ2a myocardial infarction	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good

Note: The references are available in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question.

## Appendix F4. Quality Assessment of Trials

Author, year	KQ	Random-ization	Concealed treatment allocation	Baseline group similarity	Patient blinded	Care provider blinded	Outcome assessor blinded	Counter-ventions avoided or similar	Compli-ance accept-able in all groups	Attrition reported	Attrition accept-able	Timing of outcome assess-ment in all groups similiar	Intention to treat analysis	Avoid-ance of selective outcomes reporting	Quality
Allan, 2005	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair
Ashburn, 2011	KQ3h	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cowan, 2005	KQ3i	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	no	Unclear	Yes	Yes	Unclear	Poor
Davies, 2011	KQ3h	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Jamison, 1998	KQ3a	Unclear	Unclear	Unclear	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Mitra, 2013	KQ3c	Yes	No	Unclear	Unclear	No	Yes	Yes	No	Yes	No	Yes	No	No	Poor
Naliboff 2011	KQ3f	Yes	Yes	Yes	Yes	No	Unclear	Yes (similar in both groups)	Unclear	Yes	No	Yes	Yes	Yes	Fair
Portenoy, 2007	KQ3h	Yes	Yes	NA	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Good
Ralphs, 1994	KQ3j	No	No	No	No	No	No	yes	unclear	No	Unclear	yes	yes	unclear	Poor
Salzman, 1999	KQ3a	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Simpson, 2007	KQ3h	Yes	Unclear	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tennant, 1982	KQ3j	No	No	No	No	No	No	Unclear	Unclear	No	Unclear	Yes	Yes	Unclear	Poor
Webster, 2013	KQ3h	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Wild 2010	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair

Note: The references are available in Appendix C.

Based on Cochrane Back Review Group Quality Assessment Methods (see Methods section for details).

KQ=key question.

## Appendix F5. Quality Assessment of Screening Instrument Studies

<b>Author, year</b>	<b>Evaluates population other than the one used to derive the instrument</b>	<b>Avoided case-control design</b>	<b>Consecutive series of patients or a random subset</b>	<b>Describes severity of symptoms, opioid dose/duration and underlying conditions</b>	<b>Adequate description of screening instrument</b>	<b>Appropriate criteria included in screening instrument</b>	<b>Adequate description of methods for identifying aberrant drug-related behaviors</b>	<b>Appropriate criteria used to identify aberrant drug-related behaviors</b>	<b>Aberrant drug-related behaviors assessed in all enrollees</b>	<b>Blinded assessment of aberrant drug-related behaviors</b>	<b>Quality</b>
Akbik 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Fair
Jones 2012	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Unclear	Poor
Moore 2009	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Unclear	Poor
Webster 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	Fair

Note: The references are available in Appendix C.

Based on various methods sources (see Methods section for details).

## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
<b>1. Effectiveness and comparative effectiveness</b>							
a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
b. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?							
Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient

## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
<b>2. Harms and adverse events</b>							
a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: 1) opioid abuse, addiction, and related outcomes; 2) overdose; and 3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?							
Abuse, addiction	10 uncontrolled studies (n=3,780)	High	Inconsistent	Direct	Precise	Undetected	Insufficient
Overdose	1 cohort study (n=9,940)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Fractures	1 cohort study (n=2,341) and 1 case-control study (21,739 cases)	Moderate	Consistent	Direct	Precise	Undetected	Low
Myocardial infarction	1 cohort study (n=426,124) and 1 case-control study (11,693 cases)	Low	Consistent	Direct	Precise	Undetected	Low
Endocrine	1 cross-section study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	No studies	-	-	-	-	-	Insufficient
b. How do harms vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); 2) patient demographics; 3) patient comorbidities (including past or current substance use disorder or at high risk for addiction)?							
Various harms	No studies	-	-	-	-	-	Insufficient

## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
b. How do harms vary depending on the dose of opioids used?							
Overdose	1 cohort study (n=9,940) and 1 case-control study (593 cases in primary analysis)	Moderate	Consistent	Direct	Precise	Undetected	Low
Fracture	1 cohort study (n=2,341)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low
Myocardial infarction	1 cohort study (n=426,124)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Motor vehicle accidents	1 case-control study (5,300 cases)	Low	Unknown (1 study)	Direct	Precise	Undetected	Low
Endocrine	1 cross-sectional study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low

### 3. Dosing strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

Pain	2 randomized trials (n=93)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient

b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
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## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?							
Pain and function	3 randomized trials (n=1,850)	Moderate	Consistent	Direct	Precise	Undetected	Low
Assessment of risk of overdose, addiction, abuse, or misuse	No studies	-	-	-	-	-	Insufficient
Overdose (as indicated by all-cause mortality)	1 cohort study (n=108,492)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low
Abuse and related outcomes	1 cohort study (n=5,684)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of maximum dose ceilings on outcomes related to pain, function, and quality of life?							
Pain, function, withdrawal due to opioid misuse	1 randomized trial (n=140)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low

## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?							
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?							
Pain	5 randomized trials (n=802)	Moderate	Consistent	Direct	Precise	Undetected	Moderate
Function, quality of life, abuse and related outcomes	No studies	-	-	-	-	-	Insufficient
i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal symptoms?							
Pain, function	1 randomized trial (n=10)	High	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient
j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?							
Opioid abstinence	2 nonrandomized trials (n=150)	High	Consistent	Direct	Imprecise	Undetected	Insufficient

## Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
<b>4. Risk assessment and risk mitigation strategies</b>							
a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?							
Diagnostic accuracy: Opioid Risk Tool	3 studies of diagnostic accuracy (n=496)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain version 1	2 studies of diagnostic accuracy (n=203)	High	Consistent	Direct	Imprecise	Undetected	Low
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including 1) opioid management plans, 2) patient education, 3) urine drug screening, 4) use of prescription drug monitoring program data, 5) use of monitoring instruments, 6) more frequent monitoring intervals, 7) pill counts, and 8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient
d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?							
Outcomes related to abuse	No studies	-	-	-	-	-	Insufficient