Appendixes
Appendix A. Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

Key Questions 1-3
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"
17. limit 16 to (comparative study or controlled clinical trial or randomized controlled trial)
18. exp cohort studies/
19. cohort$.tw.
20. controlled clinical trial.pt.
21. epidemiologic methods/
22. limit 21 to yr=1966-1989
23. exp case-control studies/
24. (case$ and control$).tw.
25. or/18-20,22-24
26. randomized controlled trial.pt.
27. (random* or placebo* or control* or trial or blind*).ti,ab.
28. (animals not humans).sh.
29. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
30. (26 or 27) not (28 or 29)
31. 16 and (25 or 30)
32. 17 or 31
33. limit 16 to (meta analysis or systematic reviews)
34. review.pt.
35. (medline or medlars or embase or pubmed or cochrane).tw,sh.
36. (scisearch or psychinfo or psycinfo).tw,sh.
37. (psychlit or psyclit).tw,sh.
38. cinahl.tw,sh.
39. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
40. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
41. (pooling or pooled or mantel haenszel).tw,sh.
42. (peto or dersimonian or der simonian or fixed effect).tw,sh.
43. or/35-42
44. 34 and 43
45. meta-analysis.pt.
46. meta-analysis.sh.
47. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
48. (systematic$ adj5 review$).tw,sh.
49. (systematic$ adj5 overview$).tw,sh.
50. (quantitativ$ adj5 review$).tw,sh.
51. (quantitativ$ adj5 overview$).tw,sh.
52. (quantitativ$ adj5 synthesis$).tw,sh.
53. (methodologic$ adj5 review$).tw,sh.
54. (methodologic$ adj5 overview$).tw,sh.
55. (integrative research review$ or research integration).tw.
56. or/45-55
57. 44 or 56
58. 16 and 57
59. 33 or 58
60. 32 or 59

**Key Questions 4a and 4b**

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. ((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Decision Support Techniques/
18. "Predictive Value of Tests"
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"
24. "Sensitivity and Specificity"
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2014 -Current"
30. limit 29 to english language

Key Question 4c
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2014-Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia /
3. Pain /
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid /
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/
25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30
32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2014 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Key Questions 1-3
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/
or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular)
adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or
morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or
preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"

Key Questions 4a and 4b
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/
or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular)
adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Decision Support Techniques/
18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2014 -Current"
30. limit 29 to english language

Key Question 4c
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. ((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2014 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/
25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30
32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2014 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews
All Key Questions
1. chronic.ti,ab,kw.
2. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
3. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
4. opioid*.ti,ab,kw.
5. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw.
6. (or/1-3) and (4 or 5)
7. 5 not postoperative.ti.
8. limit 7 to full systematic reviews

Database: PsycINFO
All Key Questions
1. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
2. exp pain/
3. chronic.ti,ab{id.
4. 2 and 3
5. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab.
6. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
7. 1 or 4 or 5 or 6
8. exp Opiates/
9. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab{id,hw.
10. opioid*.ti,ab{id.
11. or/8-10
12. 7 and 11
13. 12 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
14. limit 13 to english language
15. limit 14 to yr="2014 -Current"
16. exp animals/
17. 15 not 16

Database: Elsevier Embase® Online

All Key Questions
('chronic pain'/exp OR 'chronic pain' OR 'arthralgia'/exp OR arthralgia OR 'back pain'/exp OR 'back pain' OR 'backache'/exp OR backache OR 'cancer pain'/exp OR 'cancer pain' OR 'headache'/exp OR headache OR 'musculoskeletal pain'/exp OR 'musculoskeletal pain' OR 'neck pain'/exp OR 'neck pain' OR 'neuralgia'/exp OR neuralgia OR 'fibromyalgia'/exp OR fibromyalgia OR 'myalgia'/exp OR myalgia) AND ('opiate'/exp OR 'opiate' OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR methadone OR morphine OR naloxone OR oxycodone OR oxymorphone OR tapentadol) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [2014-2019]/py AND 'human'/de AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'double blind procedure'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) NOT (postoperative OR intravenous OR intramuscular OR injection* OR intrathecal OR epidural OR block OR preoperative OR perioperative OR acute) AND [english]/lim
## Appendix B. Inclusion and Exclusion Criteria

### Table B-1. POCOTS

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, 1b</td>
<td>Adults (age ≥18 years) with various types of chronic pain including pregnant/breast-feeding women and patients treated with opioids for opioid use disorder 1b subgroups: (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 opioid use disorder)</td>
<td>Long- or short-acting opioids (including partial agonists and dual mechanism agents)  Exclude: Intravenous or intramuscular administration of opioids</td>
<td>Placebo or no opioid therapy</td>
<td>Pain, function, and quality of life</td>
</tr>
<tr>
<td>1c</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Long- or short-acting opioids (including partial agonists and dual action medications)  Exclude: Intravenous or intramuscular administration of opioids</td>
<td>Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclic antidepressants, acetaminophen, memantine, and cannabis] or nonpharmacologic [noninvasive])</td>
<td>Pain, function, and quality of life; doses of opioids used</td>
</tr>
<tr>
<td>1d</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic)  Exclude: Intravenous or intramuscular administration of opioids</td>
<td>Opioids or nonopioid interventions alone, including cannabis</td>
<td>Pain, function, and quality of life, doses of opioids used</td>
</tr>
<tr>
<td>Key Question</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
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<td>-------------------------------------------------------------------------------</td>
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<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2a, 2b</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol)</td>
<td>Placebo or no opioid</td>
<td>Substance misuse, substance use disorder and related outcomes, overdose, and other harms</td>
</tr>
<tr>
<td></td>
<td>2b subgroups: (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 opioid use disorder); (4) the dose of opioids used; (5) the mechanisms of actions of the opioids; and (6) use of sedative hypnotics</td>
<td>Exclude: Intravenous or intramuscular administration of opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Long- or short-acting opioids (including partial agonists and dual action medications)</td>
<td>Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclica antidepressants, acetaminophen, memantine, and cannabis] or nonpharmacologic [noninvasive])</td>
<td>Substance misuse, substance use disorder and related outcomes, overdose, and other harms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclude: Intravenous or intramuscular administration of opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic)</td>
<td>Opioids or nonopioid interventions alone, including cannabis</td>
<td>Substance misuse, substance use disorder and related outcomes, overdose, and other harms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclude: Intravenous or intramuscular administration of opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol)</td>
<td>Other opioids with different dose initiation and titration strategies</td>
<td>Pain, function, and quality of life; doses of opioids used</td>
</tr>
<tr>
<td>Key Question</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>3b</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Short-acting opioid</td>
<td>Long-acting opioid</td>
<td>Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used</td>
</tr>
<tr>
<td>3c</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Long-acting opioid</td>
<td>Other long-acting opioid</td>
<td>Pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose and other harms; doses of opioids used</td>
</tr>
<tr>
<td>3d</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Short- and long-acting opioid</td>
<td>Long-acting opioid</td>
<td>Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used</td>
</tr>
<tr>
<td>3e</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Scheduled, continuous dosing</td>
<td>As-needed dosing</td>
<td>Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose, and other harms; doses of opioids used</td>
</tr>
<tr>
<td>3f</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Opioid dose escalation</td>
<td>Dose maintenance or use of dose thresholds</td>
<td>Pain, function, and quality of life</td>
</tr>
<tr>
<td>3g</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Opioid rotation</td>
<td>Maintenance of current opioid therapy</td>
<td>Pain, function, and quality of life; doses of opioids used</td>
</tr>
<tr>
<td>3h</td>
<td>Adults (age ≥18 years) with various types of chronic pain and an acute exacerbation</td>
<td>Treatments for acute exacerbations of chronic pain</td>
<td>Other treatments for acute exacerbations of chronic pain</td>
<td>Pain, function, and quality of life</td>
</tr>
<tr>
<td>3i</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Decreasing opioid doses or of tapering off opioids</td>
<td>Continuation of opioids</td>
<td>Pain, function, and quality of life; opioid withdrawal and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)</td>
</tr>
<tr>
<td>3j</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Tapering protocols and strategies</td>
<td>Other tapering protocols or strategies</td>
<td>Pain, function, quality of life; likelihood of opioid cessation, opiate withdrawal symptoms and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)</td>
</tr>
<tr>
<td>3k</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Dosage of opioid</td>
<td>Other dose of same opioid</td>
<td>Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms</td>
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<td>Key Question</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
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<td>4a</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose</td>
<td>Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks</td>
<td>Measures of diagnostic accuracy</td>
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<td>4b</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>Use of risk prediction instruments, genetic/metabolic tests</td>
<td>Usual care or other control</td>
<td>Misuse, opioid use disorder, overdose and other harms</td>
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<td>4c</td>
<td>Adults (age ≥18 years) with various types of chronic pain</td>
<td>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, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of benzodiazepine co-prescribing and (11) co-prescribing of naloxone</td>
<td>Usual care</td>
<td>Pain, function, quality of life, misuse, opioid use disorder, overdose and other harms (including use of illicit opioids, suicidality, and anger/violence)</td>
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<td>4d</td>
<td>Adults (age ≥18 years) with various types of chronic pain and opioid use disorder</td>
<td>Treatment strategies</td>
<td>Other treatment strategies</td>
<td>Pain, function, quality of life, misuse, opioid use disorder, overdose, other harms, pain, function, and quality of life</td>
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Appendix C. List of Excluded Studies

Exclusion Codes:
2 = Background paper
3 = Paper used for contextual question
4 = Ineligible population
5 = Ineligible intervention or no intervention
6 = Ineligible comparison
7 = Ineligible outcome
8 = Ineligible setting
9 = Ineligible publication type
10 = Ineligible study design
11 = Not available in English language
12 = Outdated review article or non systematic review
13 = Inadequate duration
14 = No reference standard used for KQ 4a
15 = Poor-quality


45. Argoff CE, Kahan M, Sellers EM. Preventing and managing aberrant drug-


78. Beaudoin FL, Merchant RC, Clark MA. Prevalence and detection of prescription opioid misuse and prescription opioid use...


111. Böhme K, Likar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomised, double-


222. Coplan PM, Sessler NE, Harikrishnan V, et al. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National


308. Duale C. Prolonged use of opioids after surgery. BMJ. 2014 Feb 11;348:g1280. doi: https://dx.doi.org/10.1136/bmj.g1280. PMID: 24519538.


10.1097/mlr.0000000000000625. PMID: 27623005.


442. Grasso MA, Dezman ZDW, Grasso CT, et al. Opioid pain medication prescriptions obtained through emergency medical visits in the Veterans Health Administration. J Opioid Manag. 2017 Mar/Apr;13(2):77-84. doi:


582. Khodneva Y, Muntner P, Kertesz S, et al. Prescription opioid use and risk of coronary heart disease, stroke, and cardiovascular death among adults from a prospective...


634. Lawrence R, Mogford D, Colvin L. Systematic review to determine which validated measurement tools can be used to assess risk of problematic analgesic use in patients with chronic pain. Br J Anaesth.


641. Lee KH, Koh SA, Kim TW, et al. Compared study of efficacy and safety between oxycodone/naloxone cr and oxycodone cr in


673. Lin HT, Chen TC, Chen LC. Variation of the exposure measures for evaluating long-


non-interventional prospective study


Pergolizzi JV, Jr., Ma L, Foster DR, et al. The prevalence of opioid-related major potential drug-drug interactions and their impact on health care costs in chronic pain...


C-62


1089. Takouche B, Montes-Martínez A, Gill SS, et al. Psychotropic medications and the risk...


1101. Thomas JR. Elucidating the molecular and biophysical determinants that suppress CA2+-dependent facilitation of CAV2.2 CA2+ channels. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;79(11-B(E)):No Pagination Specified.


1122. Ueberall MA, Mueller-Schwefe GH. Safety and efficacy of oxycodone/naloxone vs.


1186. Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine


1201. Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with


1214. Ziegler SJ. The proliferation of dosage thresholds in opioid prescribing policies and their potential to increase pain and opioid-related mortality. Pain Med. 2015 Oct;16(10):1851-6. doi:
Appendix D. Quality Rating Criteria

Randomized Controlled Trials

Selection Bias

- Randomization Sequence Generation: Is the method used to generate the allocation sequence described in sufficient detail to allow an assessment of whether it should produce comparable groups?
- Allocation Concealment: Is the method used to conceal the allocation sequence described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment?

Performance Bias

- Blinding of Participants and Personnel: Are the measures used to blind study participants and personnel from knowledge of which intervention a participant received adequate to ensure blinding was effective?

Detection Bias

- Blinding of Outcome Assessments: Are measures used to blind outcome assessors from knowledge of which intervention a participant received adequate to ensure the intended blinding was effective.

Attrition Bias

- Incomplete Outcome Data: To what degree do missing data and attrition likely affect outcomes (20% overall or differential between groups is considered high risk)?

Reporting Bias

- Selective Reporting: Do authors pre-specify outcomes and report findings for all outcomes?

Other Sources of Bias

- State any important concerns about bias not addressed in other domains. Primarily assessed on concerns of contamination, confounding, and baseline differences.

Selections for each criteria included: Yes, No, and Unclear.

Observational Studies

Criteria:

• Initial assembly of comparable groups:
• Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
• Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
• Important differential loss to followup or overall high loss to followup
• Measurements: equal, reliable, and valid (includes masking of outcome assessment)
• Clear definition of interventions
• All important outcomes considered
• Adjustment for potential confounders

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies are graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. I

Poor: Studies are graded “poor” if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.
Diagnostic Accuracy Studies

Patient Selection
- Was a consecutive or random sample of patients enrolled?
- Was a case-control design avoided?
- Did the study avoid inappropriate exclusions?

Index Test(s)
- Were the index test results interpreted without knowledge of the results of the reference standard?
- If a threshold was used, was it pre-specified?

Reference Standard
- Is the reference standard likely to correctly classify the target condition?
- Were the reference standard results interpreted without knowledge of the results of the index test?

Flow and Timing
- Was there an appropriate interval between index test(s) and reference standard?
- Did all patients receive a reference standard?
- Did patients receive the same reference standard?
- Were all patients included in the analysis?

Response options for all questions: Yes, no, unclear, or not applicable

Overall rating options: Good, fair, or poor

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (>100) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a “medium” spectrum of patients (i.e. applicable to most screening settings).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Source: Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) Criteria
Appendix E. Detailed Statistical Methods

- For followup score, missing standard deviation (SD) was imputed by assuming constant coefficient of variation (CV) across included studies.
- For change score, it is not appropriate to assume constant CV to impute missing SD given variability in treatment effects among studies. Instead,
  - If baseline mean and SD were available, we imputed followup SD assuming constant CV and calculated SD for change score assuming rho = 0.5
  - If baseline mean was available and SD was not, we imputed followup SD assuming constant CV and used it as change score SD (This is equivalent to assuming the same baseline and followup SD, and calculating SD for change score assuming rho = 0.5.)
  - If both baseline mean and SD were not available, we imputed change score SD as the average of follow up SD of other studies for the same outcome.
- The imputed values were based on all available data from the same outcome, which did not appear to vary much by type of pain or opioid.
Appendix F. List of Included Studies


56. Hale M, Tudor IC, Khanna S, et al. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic,


## Appendix G. Quality Tables

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<td>Yes/Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Fair</td>
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</tbody>
</table>

Abbreviations: ITT=intention-to-treat; NA=not applicable.
See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders (i.e., age, sex, other medications)?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article report attrition or missing data?</th>
<th>Is there important differential loss to followup or overall high loss to followup or missing data?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders (i.e., age, sex, other medications)?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
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<td>Sun, 2017</td>
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<td>Author, year</td>
<td>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?</td>
<td>Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?</td>
<td>Did the study use accurate methods for ascertaining exposures and potential confounders (i.e., age, sex, other medications)?</td>
<td>Were outcome assessors and/or data analysts blinded to the exposure being studied?</td>
<td>Did the article report attrition or missing data?</td>
<td>Is there important differential loss to followup or overall high loss to followup or missing data?</td>
<td>Did the study perform appropriate statistical analyses on potential confounders (i.e., age, sex, other medications)?</td>
<td>Were outcomes prespecified and defined, and ascertained using accurate methods?</td>
<td>Quality rating</td>
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<td>Yes</td>
<td>Fair</td>
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Abbreviations: NA=not applicable.

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

See Appendix F. Included Studies for full citations
Table G-3. Quality Assessments of Case-control Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enroll all or random sample of cases using predefined criteria?</th>
<th>Were the controls derived from the same population as the cases?</th>
<th>Were the groups comparable at baseline on key prognostic factors?</th>
<th>Were enrollment rates similar in cases and controls invited to participate?</th>
<th>Did the study use accurate methods for identifying outcomes?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Quality rating</th>
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<tbody>
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<td>Unclear</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Gomes, 2017</td>
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<td>NA</td>
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<td>Yes</td>
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<td>Gomes, 2018</td>
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<td>NA</td>
<td>Yes</td>
<td>Yes</td>
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<td>Li, 2013a</td>
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<td>Yes</td>
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<td>Li, 2013b</td>
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Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

See Appendix F. Included Studies for full citations
### Table G-4. Quality Assessments of Cross-sectional Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were outcome assessors blinded to patient characteristics?</th>
<th>Did the article report attrition?</th>
<th>Is there overall high loss to followup?</th>
<th>Were prespecified outcomes assessed in all patients?</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td>Deyo, 2013</td>
<td>Yes</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: NA=not applicable.

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

See Appendix F. Included Studies for full citations
Table G-5. Quality Assessments of Diagnostic accuracy Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Evaluates population other than the one used to derive the instrument</th>
<th>Avoided case-control design</th>
<th>Consecutive series of patients or a random subset</th>
<th>Describes patient demographics, opioid prescribing characteristics, and underlying conditions</th>
<th>Adequate description of screening instrument</th>
<th>Appropriate criteria included in screening instrument</th>
<th>Adequate description of methods for identifying aberrant drug-related behaviors</th>
<th>Appropriate criteria used to identify aberrant drug-related behaviors</th>
<th>Aberrant drug-related behaviors assessed in all enrollees</th>
<th>Blinded assessment of aberrant drug-related behaviors</th>
<th>Quality rating</th>
</tr>
</thead>
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<tr>
<td>Akbik, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Fair</td>
</tr>
<tr>
<td>Jones, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Unclear</td>
<td>Poor*</td>
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<tr>
<td>Jones, 2014</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Unclear</td>
<td>Poor</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Webster, 2005</td>
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<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Fair</td>
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</tbody>
</table>

*Jones, 2013 also downgraded because ~40% of population evaluated for predictive accuracy did not receive opioids and discrepancies in study in reported sensitivity and specificity Based on various methods sources (see Methods section for details). See Appendix F. Included Studies for full citations
## Table H-1. Key Question 1: Long-term cohort study of opioids versus placebo for chronic pain – study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Enrolled Analyzed Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veiga, 2018</td>
<td>Prospective cohort study conducted at 4 multidisciplinary chronic pain centers in Portugal</td>
<td>Pain condition: Mixed Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded Substance use: Excluded from those analyzed Prior opioid use: Not specified</td>
<td>A. Opioid users A vs. B Aged 18 to 45 years: 18.9% vs. 14.1% Aged 45 to 60 years: 31.3% vs. 31.7% Aged 60 to 75 years: 35.4% vs. 34.6% Aged &gt;75 years: 14.5% vs. 19.6% Female: 74.2% vs. 71.1% Pain duration, median (IQR): 4.0 (2.0 to 10) vs. 5.0 (2.0 to 14) years</td>
<td>Used propensity score matching to match cases (opioid users) with controls (non-users). Before and after sample matching, nonparametric and parametric tests performed; chi-square tests used for categorical variables.</td>
<td>A vs. B Enrolled: 674 Analyzed: 488 (371 vs. 117)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IQR=interquartile range.

See Appendix F. Included Studies for full citations.
Table H-2. Key Question 1: Long-term cohort study of opioids versus placebo for chronic pain – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veiga, 2018</td>
<td>Variables for the propensity score model included: sex, age, pain duration (in years), educational status/ professional activity, pain type, anxiety, depression, diabetes mellitus, dyslipidemia, cardiac disease, chronic respiratory disease, hypertension, obesity, alcohol and drug consumption, S-TOPS questionnaire dimensions at baseline, BPI interference and severity scores at baseline</td>
<td>A vs. B, proportion with clinical improvement from baseline BPI interference scale: 62.3% (231/371) vs. 67.5% (79/117) at 12 months, RR 0.92 (95% CI, 0.79 to 1.07); 57.4% (222/371) vs. 62.3% (73/117) at 24 months, RR 0.96 (95% CI, 0.81 to 1.13) BPI severity scale: 61.5% (228/371) vs. 76.1% (89/117) at 12 months, RR 0.81 (95% CI, 0.71 to 0.92); 53.4% (198/371) vs. 59.0% (69/117) at 24 months, RR 0.90 (95% CI, 0.76 to 1.08) S-TOPS Pain symptoms: 66.8% (248/371) vs. 76.9% (90/117) at 12 months, RR 0.87 (95% CI, 0.77 to 0.98); 57.1% (221/371) vs. 71.7% (85/117) at 24 months, RR 0.82 (95% CI, 0.71 to 0.94) S-TOPS Physical function of lower body: 38.8% (144/371) vs. 50.4% (59/117) at 12 months, RR 0.77 (95% CI, 0.62 to 0.96); 45.5% (169/371) vs. 36.7% (43/117) at 24 months, RR 1.24 (95% CI, 0.95 to 1.61) S-TOPS Physical function of upper body: 47.9% (70/371) vs. 60.9% (23/117) at 12 months, RR 0.96 (95% CI, 0.63 to 1.46); 20.2% (75/371) vs. 14.5% (17/117) at 24 months, RR 1.39 (95% CI, 0.86 to 2.26) S-TOPS Satisfaction with outcome: 67.6% (251/371) vs. 53.8% (63/117) at 12 months, RR 0.12 (95% CI, 0.08 to 0.19); 64.4% (239/371) vs. 47.0% (55/117) at 24 months, RR 1.37 (95% CI, 1.11 to 1.68) S-TOPS Satisfaction with care: 60.9% (226/371) vs. 47.9% (56/117) at 12 months, RR 1.27 (95% CI, 1.03 to 1.56); 56.3% (209/371) vs. 46.1% (54/117) at 24 months, RR 1.22 (95% CI, 0.98 to 1.51) S-TOPS Family/social disability: 45.5% (176/371) vs. 53.2% (63/117) at 12 months, RR 0.88 (95% CI, 0.72 to 1.07); 46.0% (169/371) vs. 47.0% (55/117) at 24 months, RR 0.97 (95% CI, 0.77 to 1.21) S-TOPS Role emotional disability: 42.3% (157/371) vs. 41.0% (48/117) at 12 months, RR 1.03 (95% CI, 0.80 to 1.32); 33.7% (125/371) vs. 41.9% (49/117) at 24 months, RR 0.80 (95% CI, 0.62 to 1.04)</td>
<td>North Portugal Regional Operational Programme and the European Regional Development Fund</td>
<td>Good</td>
</tr>
</tbody>
</table>

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; IQR=interquartile range; RR=relative risk; S-TOPS=Shortened Treatment Outcomes in Pain Survey. See Appendix F. Included Studies for full citations.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell, 2018</td>
<td>Prospective cohort, recruited through community pharmacies, Australia</td>
<td>Adults, chronic (&gt;3 months) non-cancer pain, prescribed opioids (fentanyl, morphine, oxycodone, buprenorphine, methadone, hydromorphone) for &gt;6 weeks. Excluded: prescribed opioids for opioid substitution therapy for heroin dependence or those with cancer</td>
<td>A. Near daily or daily use (&gt;20 days/month): 3% at baseline  B. Less frequent use (1 to 19 days/month): 5% at baseline  C. No cannabis use: 91% at baseline</td>
<td>Age, median (IQR), years: 58 (48 to 67)  Female: 56%  Back or neck pain: 77%  Arthritis: 62%  Neuropathic pain: 62%  Duration of chronic pain, median (IQR): 10 (4.5 to 20.0) years  Baseline BPI Pain Severity Score, mean (SD): 5.1 (1.8)  Baseline BPI Pain Interference Score, mean (SD): 5.7 (2.3)  Duration prescribed strong opioid, median (IQR): 4 (1.5 to 10.0) years  Baseline oral morphine equivalents, median mg/day (IQR): 75 (36 to 150)  Baseline cannabis lifetime use: 43%  # of pain conditions, median (IQR): 2 (2 to 3)  Unemployed: 49%  Retired: 31%</td>
<td>Phone interviews and self-completed surveys</td>
<td>Screened: 2091  Eligible: 1873  Enrolled: 1514  Analyzed: 1235 at 1 year, 1277 at 2 years, 1211 at 3 years, 1217 at 4 years</td>
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<tr>
<td>Vigil, 2017</td>
<td>Historical cohort, Single physician single rehabilitation clinic, New Mexico Medical Cannabis Program (MCP)</td>
<td>Adults, enrolled at rehabilitation clinic; at least 2 opioid prescriptions in 3 months prior to start of observation period; prescribed &lt; 200 mg/day IV morphine equivalents Excluded: Inflammatory conditions (such as rheumatoid arthritis)</td>
<td>A. Self-referral to MCP with diagnosis of &quot;severe chronic pain&quot; from musculoskeletal condition annually validated by 2 independent physicians (n=37)  B. Non-MCP patients with diagnosis of common chronic back pain condition with no current usage of cannabis (n=29)</td>
<td>A. Age, mean (SD), years: 53.6 (9.5)  Male 45.9%  Back pain 86%  Knee pain 5%  Hip pain 3%  Wrist pain 3%  Shoulder pain 3%  Daily opioid dosage 1st 3 months, mean (SD): 24.4 mg (23.3)  B. Age, mean (SD), years: 59.7 (13.8)  Female 31%  Back pain 100%  Daily opioid dosage 1st 3 months, mean (SD): 16.2 mg (14.8)</td>
<td>New Mexico Prescription Monitoring Program and self-completed surveys (only completed by MCP patients)</td>
<td>Screened: 146  Screened: 53  Eligible/Enrolled: 37  Eligible/Enrolled: 29  Analyzed: 37  Analyzed: 29  Completed survey: 33</td>
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</tbody>
</table>

Abbreviations: BPI=Brief Pain Inventory; IQR=interquartile range; IV=intravenous; mg=milligram; MCP=medical cannabis program; SD=standard deviation.

See Appendix F. Included Studies for full citations
### Table H-4. Key Question 1: Studies of cannabis use in patients prescribed opioids for chronic pain – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell, 2018</td>
<td>Outcome at previous year, age sex, duration of pain, generalized anxiety disorder severity, history of substance use, and pain self-efficacy; pain severity adjusted for oral morphine equivalent, pain interference adjusted for pain severity and oral morphine equivalent, and oral morphine equivalent adjusted for pain severity</td>
<td>A vs. B vs. C</td>
<td>National Health and Medical Research Council &amp; Australian Government</td>
<td>Fair</td>
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<tr>
<td>Campbell, 2018</td>
<td></td>
<td>BPI pain severity score, mean (SE): 5.2 (0.14) vs. 5.1 (0.13) vs. 4.9 (0.03) compared to previous wave, p=0.20 for A vs. C and p=0.06 for B vs. C</td>
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<tr>
<td>Campbell, 2018</td>
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<td>BPI pain interference, mean (SE): 5.2 (0.19) vs. 5.7 (0.16) vs. 5.4 (0.04) compared to previous wave, p=0.13 for A vs. C and p=0.23 for B vs. C</td>
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<tr>
<td>Vigil, 2017</td>
<td>Control for age and gender</td>
<td>A vs. B</td>
<td>University of New Mexico Cannabis Research Fund</td>
<td>Fair</td>
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<tr>
<td>Vigil, 2017</td>
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<td>Ceased opioid prescriptions: 40.5% (15/37) vs. 3.4% (1/29), p&lt;0.001; OR (95% CI): 17.27 (1.89 to 157.36)</td>
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<td>Vigil, 2017</td>
<td></td>
<td>Reduced prescribed daily opioid: 83.8% (31/37) vs. 44.8% (13/29), p=0.001; OR (95% CI): 5.12 (1.56 to 16.88)</td>
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<tr>
<td>Vigil, 2017</td>
<td></td>
<td>Change in prescribed daily opioid dosage (mg), mean (SD): -12.0 (23.4) vs. -3.9 (13.2) (p=0.101)</td>
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<tr>
<td>Vigil, 2017</td>
<td></td>
<td>Percent point change in prescribed daily opioid dosage, mean (SD): -47.0% (63.1) vs. 10.4% (114.9) (p=0.013)</td>
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</table>

**Abbreviations**: BPI=Brief Pain Inventory; CI=confidence interval; mg=milligrams; GAD=Generalized Anxiety Disorder; OR=odds ratio; RR=risk ratio; SD=standard deviation; SE=standard error.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study Setting</th>
<th>Eligibility Criteria</th>
<th>Population Characteristics</th>
<th>Opioid Dose, Duration, and Indication</th>
<th>Method of Ascertaining and Defining Abuse/Misuse</th>
<th>Main Results</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Adams, 2006</td>
<td>Prospective cohort, Setting not described</td>
<td>Patients aged 18 to 74 years, initiating a new therapy of NSAIDs, hydrocodone, or tramadol, with pain lasting ≥4 months</td>
<td>n=11,352 Age 18 to 35 years: 13.2% Age 36 to 50 years: 36.1% Age 51 to 65 years: 33.9% Age ≥66 years: 16.8% Female: 68.2% White: 84.0% Black: 12.7% Asian: 0.4% Native American: 1.1% Other race: 1.7%</td>
<td>Dose: NR Duration: NR overall Indication: 19.9% osteoarthritis, 16.6% other disorders of the back, 10.0% other disorders of the soft tissue, 8.0% other/unspecified joint disorders, 6.3% rheumatoid arthritis, 15.6% disc, knee, and cervical disorders</td>
<td>Abuse index (inappropriate use, use for purposes other than intended, inability to stop use, and evidence of opioid withdrawal)</td>
<td>Hydrocodone (n=4278) vs. tramadol (n=4965) vs. NSAID (n=8589) Cases of abuse: 4.9% (208/4278) vs. 2.7% (133/4965) vs. 2.5% (218/8589), p&lt;0.01</td>
<td>Fair</td>
</tr>
<tr>
<td>Bedson, 2019</td>
<td>Prospective cohort UK Clinical Practice Research Datalink primary care database</td>
<td>Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition</td>
<td>N=98,140 Median (IQR) age, years: 61 (47 to 73) Female: 59%</td>
<td>Dose: median average daily dose of 12.3 mg MED Duration: median 3.4 years (IQR 1.5 to 5.8) Indication: musculoskeletal pain</td>
<td>Unclear</td>
<td>Long-term opioid use vs. not on long-term opioid Cases of abuse: 142 vs. 90 Adjusted HR (95% CI), not on long-term opioid as reference Overall for all long-term opioid users: 2.83 (2.13 to 3.76) &lt;20 mg MED/day: 1.06 (0.71 to 1.60) 20 to &lt;50 mg MED/day: 3.59 (2.55 to 5.06) ≥50 mg MED/day: 9.33 (6.55 to 13.29)</td>
<td>Fair</td>
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<tr>
<td>Author, Year</td>
<td>Type of Study</td>
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<td>Eligibility Criteria</td>
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<td>Edlund, 2014</td>
<td>Retrospective HMO, PPO and point-of-service 2000-2005 database review, United States</td>
<td>Patients aged ≥18 years with a new chronic non-cancer pain diagnosis, no cancer diagnosis, and no opioid use or opioid use disorder diagnosis in prior 6 months</td>
<td>n=568,640 (197,269 prescribed opioids in first year; of these, 5.5% had chronic use, &gt;90-days supply) Mean age not reported; 11% age 18 to 30, 20% age 31 to 40, 27% age 41 to 50, 30% age 51 to 64, 12% ≥ age 65 Female: 58% Race: NR Mean duration of pain: all patients newly diagnosed</td>
<td>Dose: Among those with any opioid use, median = 36 mg/day MED. Daily MED categorized as none, low (1 to 36 mg), medium (36 to 120 mg), or high (≥120 mg). Duration: Mean NR; users identified as &quot;chronic&quot; had ≥91 days Indication: NR; inclusion criteria required newly diagnosed chronic non-cancer pain</td>
<td>Diagnosis of opioid abuse or dependence (ICD-9-CM code 304.00 or 305.50) within 18 months of first chronic non-cancer pain diagnosis</td>
<td>Opioid abuse or dependence No opioid prescription: 0.004% (150/371,371) Low dose, chronic: 0.72% (50/6902) Medium dose, chronic: 1.28% (47/3654) High dose, chronic: 6.1% (23/378) Abuse or dependence, opioid use vs. no use Low dose, chronic: aOR* 15 (95% CI, 10 to 21) Medium dose, chronic: aOR 29 (95% CI, 20 to 41) High dose, chronic: aOR 122 (95% CI, 73 to 206)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; CM=clinical modification; HMO=health management organization; HR=hazard ratio; ICD=international classification of disease; IQR=interquartile range; MED=morphine equivalent dose; mg=milligrams; NR=not reported; OR=odds ratio; NSAID=nonsteroidal antiinflammatory drug; PPO=preferred provider organization; UK=United Kingdom; vs.=versus.  *Adjusted for age, sex, number of tracer pain sites, number of nonsubstance mental health disorders, previous substance abuse or dependence diagnosis, Charlson score.  See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
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<tr>
<td>Bedson, 2019</td>
<td>Prospective cohort U.K. Clinical Practice Research Datalink primary care database</td>
<td>Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition</td>
<td>A. Long-term opioid use 1. &lt;20 mg MED/day 2. 20 to &lt;50 mg MED/day 3. ≥50 mg MED/day B. No long-term opioid used</td>
<td>Median (IQR) age, years: 61 (47 to 73) Female: 59%</td>
<td>Unclear</td>
<td>Enrolled: 98,140 Analyzed: 98,140</td>
</tr>
<tr>
<td>Bohnert, 2016</td>
<td>Nested case-control</td>
<td>VHA patients with a chronic pain diagnosis (by ICD-9 codes) who were prescribed an opioid on the index date (a new prescription with at least a 2-year gap since last prescription episode) and who filled the prescription at a VHA facility.</td>
<td>Cases: died of an opioid-related overdose (unintentional or unknown) (n=399 matched a control) Controls: random sample from a serious mental illness registry who received opioids (n=483,278)</td>
<td>Mean age, years: 48.4 Female: 2.3% White: 86.9% Charlson comorbidity index Score of 0: 70.1% Score of 1: 17.7% Score of 2: 12.2%</td>
<td>Controls matched on sex, age, race and ethnicity, substance use disorder diagnosis, depression, other psychiatric diagnosis, acute pain, comorbid chronic diseases, Charlson score, use of benzodiazepines, antidepressants, and anticonvulsants, and ≥90 days of continuous opioid use at index date.</td>
<td>Cases Enrolled: 399, 221 matched to controls Controls Analyzed: 483,278 Loss to followup: None</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Type of Study, Setting</td>
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<tr>
<td>Dunn, 2010</td>
<td>Retrospective cohort, Group Health United States</td>
<td>Age &gt;18 years starting new episode of opioid use (no opioids in past 6 months) from 1997 to 2005; having ≥3 opioid scripts filled in first 90 days of episode; diagnosis of chronic noncancer pain in 2 weeks before first opioid script.</td>
<td>Morphine equivalent doses: A. 1 to &lt;20 mg/day B. 20 to &lt;49 mg/day C. 50 to &lt;99 mg/day D. ≥100 mg/day</td>
<td>Mean (SD; range) age, years: 54 (16.8; 18 to 99) Female: 59.6% Race: NR 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% Charlson Score, mean (SD; range): 0.71 (1.48; 0 to 14) Smoking: 29.5% Depression: 26.9% Substance abuse: 6.2% 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%</td>
<td>All patients in HMO meeting inclusion criteria</td>
<td>Enrolled: 9940 Analyzed: 9940 Loss to followup: 32% left cohort during study; 7% died Mean duration of followup (range): 42 months (&lt;1 to 119)</td>
</tr>
<tr>
<td>Gomes, 2011</td>
<td>Case-control, Canada</td>
<td>Residents aged 15 to 64 years with public drug coverage and an opioid for nonmalignant pain (1997 to 2006)</td>
<td>Cases: Died of an opioid-related cause (n=498 matched a control) Controls: received opioids (n=1714) A. 1 to &lt;20 mg/day B. 20 to &lt;50 mg/day C. 50 to &lt;100 mg/day D. 100 to &lt;200 mg/day E. ≥200 mg/day</td>
<td>Total cohort n= 607,156 Mean (SD) age, years: 44.49 (8.25) cases, 44.72 (8.20) controls Sex (NR male or female): 58.8% cases, 58.0% controls</td>
<td>Controls matched on disease risk index (0.2 SD caliper), age, gender, index year, and Charlson</td>
<td>Primary-analysis: 593 with 498 matched Secondary-analysis: 873 with 781 matching</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Type of Study, Setting</td>
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<td>Population Characteristics</td>
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</table>
| Ray, 2016    | Retrospective cohort Tennessee Medicaid enrollees | Patients initiating therapy with the study drugs who had a diagnosis of chronic pain in the past 90 days | A. Long-acting opioid (morphine SR, oxycodone CR, transdermal fentanyl, methadone) B. Anticonvulsant or cyclic antidepressant | A vs. B  
Mean (SD) age, years: 47.9 (10.5) vs. 47.9 (107)  
Female: 60% vs. 60%  
Back pain: 75% vs. 76%  
Other musculoskeletal pain: 63% vs. 64%  
Abdominal pain: 18% vs. 18%  
Headache: 12% vs. 12%  
Other neurologic pain: 17% vs. 16% | Hospital death was defined as occurring if patients were admitted to the hospital on a day during which they had used one of the study drugs and died either while in the hospital or within 30 days of admission. All other deaths were considered out-of-hospital deaths (including patients who died in the emergency department) and were further classified as unintentional medication overdose or other deaths. The latter included cardiovascular, respiratory, other injury, or other deaths.  
Enrolled: 45,824  
(22,912 vs. 22,912)  
Analyzed: 45,824  
(22,912 vs. 22,912) |

Abbreviations: HMO=health management organization; MED=morphine equivalent dose; NR=not reported; SD=standard deviation; SR=sustained release; U.K.=United Kingdom; VHA=Veterans Health Administration; vs.=versus.  
See Appendix F. Included Studies for full citations.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedson, 2019</td>
<td>Age, sex, year of start of followup, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m²), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID, and total number of co-morbid conditions.</td>
<td>Incidence of opioid overdose (A vs. B): 11.6 vs. 4.8 per 10,000 person-years Incidence of attempted suicide/self-harm (A vs. B): 0.7 vs. 0.6 per 10,000 person-years Attempted suicide/self-harm for A with B as reference: 1.01 (0.42 to 2.45) Adjusted HR (95% CI) of opioid overdose (B as reference) A: 2.24 (1.73 to 2.89) 1: 1.59 (1.16 to 2.19) 2: 2.83 (2.04 to 3.92) 3: 3.81 (2.50 to 5.80)</td>
<td>Unclear</td>
<td>Fair</td>
</tr>
<tr>
<td>Bohnert, 2016</td>
<td>Sex, age, race and ethnicity, substance use disorder diagnosis, depression, other psychiatric diagnosis, acute pain, comorbid chronic diseases, Charlson score, use of benzodiazepines, antidepressants, and anticonvulsants, and ≥90 days of continuous opioid use at index date.</td>
<td>Cases vs. controls Mean (SD) prescribed dose: 98.1 MEM (112.7) vs. 47.7 MEM (65.2), p&lt;0.001 Median (IQR) prescribed dose: 60 MEM (30 to 120) vs. 25 MEM (15 to 45) Opioid dose was a good predictor of cases versus controls: ROC curve analysis: AUC 0.71 (95% CI, 0.66 to 0.76), p&lt;0.001 Hosmer to Lemeshow goodness of fit, week 2 :13.37, ps0.01</td>
<td>CDC and VHA</td>
<td>Good</td>
</tr>
<tr>
<td>Dunn, 2010</td>
<td>Sedative-hypnotic use as time-varying covariate Age, sex, smoking, depression diagnosis, substance abuse diagnosis, index pain diagnosis, chronic disease comorbidity adjustors (RxRisk &amp; Charlson)</td>
<td>51 patients with overdose events (148 per 100,000 person to years) 50 serious overdose events (116 per 100,000 person to years) 5 fatal overdose events (17 per 100,000 person to years) Rate of any overdose per 100,000 person to years (95% CI); HR (95% CI) No opioid: 36 (13 to 70); 0.31 (0.12 to 0.80); 6 overdose events A. (reference): 160 (100 to 233); 1.0 B. 260 (95 to 505); 1.44 (0.57 to 3.62) C. 677 (249 to 1317); 3.73 (1.47 to 9.5) D. 1791 (894 to 2995); 8.87 (3.99 to 19.72) Opioid dose, any: 256 (187 to 336); 5.16 (2.14 to 12.48); 45 overdose events HR, serious events (95% CI) No opioid: 0.19 (0.05 to 0.68) A. (reference): 1.0 B. 1.19 (0.4 to 3.6); C. 3.11 (1.01 to 9.51); D. 11.18 (4.8 to 26.03); Opioid dose, any: 8.39 (2.52 to 27.98)</td>
<td>National Institute of Drug Abuse and Wellcome Trust</td>
<td>Fair</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Adjusted Variables for Statistical Analysis</td>
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<tr>
<td>Gomes, 2011</td>
<td>Opioid exposure categorized by Average Daily Dose: &lt;20mg, 20 to 49mg, 50 to 99mg, 100 to 199mg, ≥200mg 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</td>
<td>Risk estimates reported as adjusted OR (95% CI) Risk of opioid overdose death A. 1 (reference) B. 1.32 (0.94 to 1.84) C. 1.92 (1.30 to 2.85) D. 2.04 (1.28 to 3.24) E. 2.88 (1.79 to 4.63) Secondary using 120 to day exposure window risk of opioid overdose death A. 1 (reference) B. 0.93 (0.60 to 1.42) C. 1.31 (0.86 to 1.99) D. 1.47 (0.98 to 2.19) E. 2.24 (1.62 to 3.10)</td>
<td>MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC</td>
<td>Good</td>
</tr>
<tr>
<td>Ray, 2016</td>
<td>The primary models included age, calendar year, and study medication as time-dependent covariates, estimated via a counting process formulation that accommodates nonproportional hazards</td>
<td>Adjusted HR (95% CI) A vs. B All deaths: 1.64 (1.26 to 2.12) Out-of-hospital deaths: 1.90 (1.40 to 2.58) Unintentional overdose: 3.37 (1.47 to 7.70) Out-of-hospital, not overdose death: 1.72 (1.24 to 2.39) Cardiovascular cause: 1.65 (1.10 to 2.46) Respiratory cause: 3.00 (0.81 to 11.09) Other injury cause: 1.15 (0.54 to 2.47) Other causes: 3.72 (1.04 to 13.30) In hospital deaths: 1.00 (0.59 to 1.69) All deaths in those taking high doses: 1.94 (1.40 to 2.70) All deaths in those taking low doses: 1.54 (1.01 to 2.34)</td>
<td>Government</td>
<td>Fair</td>
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</table>

Abbreviations: BMI=body mass index; CDC=Centers for Disease Control and Prevention; CI=confidence interval; EtOH=alcohol; HR=hazard ratio; ICES=Institute for Clinical Evaluative Sciences; IQR=interquartile range; MOHLTC=Ministry of Health and Long-Term Care; NSAID=nonsteroidal antiinflammatory drug; OR=odds ratio; SD=standard deviation; VHA=Veterans Health Administration; vs.=versus.
See Appendix F. Included Studies for full citations
Table H-8. Key Question 2a: Studies of long-term opioid use and fractures – study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method for Assessing Outcomes and Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedson, 2019</td>
<td>Prospective cohort U.K. Clinical Practice Research Datalink primary care database</td>
<td>Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition</td>
<td>A. Long-term opioid use 1. &lt;20 mg MED/day 2. 20 to &lt;50 mg MED/day 3. ≥50 mg MED/day  B. No long-term opioid used</td>
<td>Median (IQR) age, years: 61 (47 to 73) Female: 59%</td>
<td>Unclear</td>
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<tr>
<td>Carbone, 2013</td>
<td>Cohort VA Spinal Cord Dysfunction Registry, United States</td>
<td>All male Veterans with a traumatic spinal cord injury with at least 2 years duration. Fracture incidence and opioid use was also obtained.</td>
<td>Duration of use of opioids prior to the incident fracture, was stratified by: 0 days (reference), &lt;6 months, 6 months to ≤1 year, 1 to ≤2 years, 2 to ≤3 years, and ≥3 years, and dose stratified by &lt; 224 mg and &gt;225 mg</td>
<td>Mean age, years: 58 Female: 0% Duration of spinal cord injury &gt;10 years: 30% Charlson Comorbidity index: 3.84 Treatment for osteoporosis: 55%</td>
<td>ICD-9 codes for fractures of the lower extremity, including: femoral neck (820.x), intertrochanteric (820.21, 820.31), subtrochanteric (820.22, 820.32), pelvis (808.x), femur (820.x, 821.x), patella (822.x), and tibia/fibula (823.x). Only incident fractures were included. A fracture was considered incident (i.e. a new episode of fracture and not coding of follow-up care for a prior fracture), if there were no encounters with the same three-digit ICD-9 codes within a 120-day period prior to the fracture. They excluded 140 fractures that had received codes indicating an external cause of injury (E codes).</td>
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<td>Krebs, 2016</td>
<td>Prospective cohort 6 sites, United States</td>
<td>Men ≥65 years with back, hip, or knee pain most or all of the time</td>
<td>A. Opioid use  B. Opioid non-use</td>
<td>Mean (SD) age, years: 74.7 (6.4) vs. 73.7 (5.9) Female: 0% White: 89.2% vs. 91.9% Mean (SD) BMI: 28.8 (4.5) vs. 28.0 (4.0) Back pain: 61.2% vs. 27.6% Hip pain: 59.7% vs. 49.0% Knee pain: 65.1% vs. 67.0%</td>
<td>Falls and fractures were self-reported on questionnaires every 4 months. Fractures were confirmed by x-ray or review of imaging reports. Physical performance was assessed using tests of grip strength, chair stands, gait speed, and dynamic balance. Each individual test was scored from 0=unable to complete to 5=best and converted to quintiles based on score distributions. The individual test scores were summed to create an overall physical performance score with a possible range of 0 to 20, where lower scores indicated worse performance.</td>
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<tr>
<td>Author, Year</td>
<td>Type of Study, Setting</td>
<td>Eligibility Criteria</td>
<td>Comparison Groups</td>
<td>Population Characteristics</td>
<td>Method for Assessing Outcomes and Confounders</td>
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| Li, 2013    | Nested case control   | United Kingdom       | Cases (n=21,739): First-time diagnosed fracture of the hip, humerus, or wrist during 1990 to 2008, age 18 to 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 to 3 opioid prescriptions  
D. 4 to 5 opioid prescriptions  
E. 6 to 20 opioid prescriptions  
F. 21 to 50 opioid prescriptions  
G. 51 to 100 opioid prescriptions  
H. >100 opioid prescriptions | Mean age, years: 62  
Female: 77%  
Race: NR  
Pain condition: NR  
Pain duration: NR  
Pain severity: NR  
Mean dose: NR  
Most commonly prescribed opioids: dihydrocodeine, codeine, propoxyphene, tramadol | Used General Practice Research Database, in which drug exposures and diagnoses (including fracture) have been validated |
<table>
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<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method for Assessing Outcomes and Confounders</th>
</tr>
</thead>
</table>
| Lo-Ciganic, 2017 | Prospective cohort 4 sites, United States | Aged 45 to 79 years with or at high-risk for knee osteoarthritis | A. Opioid users  
B. Antidepressant users  
C. Prescription pain medication users  
D. Over the counter pain medication users  
E. Nutraceutical users  
F. No pain medication use | A vs. B vs. C vs. D vs. E vs. F  
Mean (SD) age, years: 60.1 (9.2) vs. 59.3 (8.7) vs. 62.8 (9.1) vs. 61.8 (8.1) vs. 61.3 (9.0) vs. 61.2 (9.3)  
Female: 71.9% vs. 74.4% vs. 59.5% vs. 57.3% vs. 52.9% vs. 53.8%  
White: 72.8% vs. 87.8% vs. 78.8% vs. 75.3% vs. 88.3% vs. 79.0%  
Mean (SD) BMI: 30.8 (5.2) vs. 29.1 (5.3) vs. 29.3 (4.8) vs. 28.9 (4.9) vs. 27.5 (4.4) vs. 28.0 (4.6)  
History of falls in previous year: 26.3% vs. 25.4% vs. 14.7% vs. 15.2% vs. 14.8% vs. 11.5%  
Mean (SD) PCS SF-12 score: 39.6 (9.9) vs. 48.4 (9.6) vs. 46.5 (9.2) vs. 47.0 (9.1) vs. 51.4 (7.6) vs. 51.7 (7.5)  
Mean (SD) MCS SF-12 score: 50.6 (10.4) vs. 49.2 (9.8) vs. 55.2 (7.4) vs. 54.0 (8.1) vs. 54.8 (7.0) vs. 54.5 (6.7)  
Mean (SD) PASE score: 146.2 (78.9) vs. 156.7 (82.8) vs. 152.5 (84.4) vs. 165.8 (84.3) vs. 169.2 (79.6) vs. 163.0 (79.4)  
Mean (SD) pain NRS: 5.0 (2.9) vs. 3.6 (2.7) vs. 3.8 (2.7) vs. 4.2 (2.7) vs. 2.8 (2.3) vs. 2.6 (2.5) | Falls were self-reported |
| Miller, 2011 | Prospective cohort New Jersey Medicare recipients, United States | Medicare beneficiaries with osteoarthritis or rheumatoid arthritis who initiated monotherapy with a NSAID or an opioid between January 1, 1999 and December 31, 2006 | A. Short-acting opioids  
B. Long-acting opioids  
C. NSAIDs  
Additional subgroups:  
D. Low-dose opioid (<75 mg equivalents of codeine/day)  
E. Medium-dose opioid (76 to 225 mg equivalents of codeine/day)  
F. High-dose opioid (>225 mg equivalents of codeine/day) | A vs. B vs. C  
Mean (SD) age, years: 81.1 (7.1) vs. 81.5 (7.7) vs. 79.7 (7.0)  
Female: 84.0% vs. 84.3% vs. 84.0%  
White: 92.6% vs. 90.1% vs. 84.6%  
History of previous fractures: 13.9% vs. 10.7% vs. 6.5%  
Osteoporosis: 31.1% vs. 35.1% vs. 29.3%  
Chronic back pain: 33.1% vs. 29.2% vs. 28.6%  
Use of benzodiazepines: 24.3% vs. 25.4% vs. 20.6% | Fractures of the hip, humerus/ulna, or wrist, identified by a combination of diagnosis (ICD-9CM codes) and procedure (CPT codes) |
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<tr>
<th>Author, Year</th>
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<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method for Assessing Outcomes and Confounders</th>
</tr>
</thead>
</table>
| Saunders, 2010 | Cohort Group Health Cooperative, United States | Age ≥60 years, initiating opioids (no opioid prescriptions in prior 6 months) with ≥3 prescriptions in 90 days and a diagnosis of non-cancer pain 2 to 3 weeks prior to the index prescription. | Opioid dose:  
A. Not currently using  
B. 1 to <20 mg/day  
C. 20 to <50 mg/day  
D. >50 mg/day  
E. Any use | Mean age, years: 73  
Female: 66%  
Race: NR  
Depression diagnosis: 22%  
Substance abuse diagnosis: 3.8%  
Dementia diagnosis: 4.8%  
Prior fracture: 2.6%  
HRT/bisphosphonate use: 34%  
Rx Risk 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 (SD) MED, mg: 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% | 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 |

Abbreviations: BMI=body mass index; CM=clinical modification; CPT=current procedural terminology; ICD=international classification of disease; IQR=interquartile range; MED=morphine equivalent dose; MCS=mental component subscale; NR=not reported; NRS=numerical rating scale; NSAID=nonsteroidal antiinflammatory drug; PCS=physical component subscale; SD=standard deviation; SF-12=short form 12-item; U.K.=United Kingdom; VA=Veterans Affairs; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Enrolled Analyzed</th>
<th>Loss to Followup</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Bedson, 2019</td>
<td>Enrolled: 98,140</td>
<td>Analyzed: 98.140</td>
<td>Age, sex, year of start of followup, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m²), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID, and total number of co-morbid conditions.</td>
<td>Incidence of falls (A vs. B): 548.9 vs. 369.5 per 10,000 person-years</td>
<td>VA</td>
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<td>Incidence of major trauma (A vs. B): 375.7 vs. 285.4 per 10,000 person-years</td>
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<td>Adjusted HR (95% CI), B as reference</td>
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<td>Falls for A: 1.23 (1.19 to 1.28)</td>
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<td>Falls for 1: 1.17 (1.12 to 1.21)</td>
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<td>Falls for 2: 1.34 (1.27 to 1.42)</td>
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<td>Falls for 3: 1.64 (1.50 to 1.80)</td>
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<td>Major trauma for A: 1.14 (1.10 to 1.19)</td>
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<td>Major trauma for 1: 1.09 (1.04 to 1.14)</td>
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<td>Major trauma for 2: 1.24 (1.16 to 1.32)</td>
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<td>Major trauma for 3: 1.34 (1.20 to 1.50)</td>
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<td>Carbone, 2013</td>
<td>Enrolled: 7447</td>
<td>Analyzed: Unclear</td>
<td>Age, race, duration of spinal cord injury, level of spinal cord injury, and completeness of spinal cord injury (complete/incomplete/unknown), Charlson comorbidity indices, Medication use that may be associated with fracture risk (including heparin, corticosteroids, loop diuretics, thiazide diuretics, proton pump inhibitors serotonin receptor agonists, thiazolidinediones), and pharmacological treatments for osteoporosis (teriparatide, bisphosphonates, calcitonin), calcium, and vitamin D.</td>
<td>Higher doses (≥225 mg/day of codeine equivalents) were significantly positively associated with fracture risk in adjusted models (p&lt;0.0001).</td>
<td>NIH</td>
<td>Fair</td>
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<td>Krebs, 2016</td>
<td>Enrolled: 2902 (390 vs. 2512)</td>
<td>Analyzed: 2732 (129 vs. 2603)</td>
<td>Propensity score matching was done based on age, BMI, total hip BMD, race/ethnicity, smoking status, current alcohol use, and health status.</td>
<td>A vs. B</td>
<td>NIH</td>
<td>Fair</td>
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<td>Loss to followup: 89 (3.1%) dropped out; overall 30.5% attrition</td>
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<td>Unadjusted RR (95% CI) of falling: 1.37 (1.23 to 1.54)</td>
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<td>Unadjusted HR (95% CI) of any clinical fracture: 1.09 (0.92 to 1.28)</td>
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<td>Unadjusted HR (95% CI) of hip fracture: 2.14 (1.36 to 3.38)</td>
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<td>Unadjusted difference (95% CI) between groups in change in physical performance score from baseline: 0.048 (-0.062 to 0.158)</td>
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<td>Adjusted PS-restricted cohort HR (95% CI) of mortality: 1.22 (0.94 to 1.58)</td>
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<td>Adjusted PS-restricted cohort HR (95% CI) of clinical fracture/death composite outcome: 1.14 (0.88 to 1.48)</td>
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<td>Adjusted PS-restricted cohort HR (95% CI) of hip fracture/death composite outcome: 1.22 (0.94 to 1.58)</td>
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<tr>
<td>Author, Year</td>
<td>Enrolled Analyzed Loss to Followup</td>
<td>Adjusted Variables for Statistical Analysis</td>
<td>Main Results</td>
<td>Funding Source</td>
<td>Quality</td>
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| Li, 2013     | 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, comedinations, types of pain, recent/past opioid use (matched on age, sex, index date, and general practice) | Adjusted OR (95% CI) for risk of hip, humerus, or wrist fracture  
A. 1 (reference)  
B. 2.70 (2.34 to 3.13)  
C. 1.90 (1.67 to 2.17)  
D. 1.44 (1.22 to 1.69)  
E. 1.17 (1.08 to 1.27)  
F. 1.06 (0.98 to 1.15)  
G. 1.06 (0.96 to 1.16)  
H. 1.12 (0.99 to 1.25)  
1. 1 (reference)  
2. 1.27 (1.21 to 1.33)  
3. 1.05 (0.99 to 1.13)  
4. 0.96 (0.92 to 1.01) | None | Good |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo-Ciganic, 2017</td>
<td>Enrolled: 4231 at 12 months, 3891 at 24 months, 3764 at 36 months, 3762 at 48 months</td>
<td>Analyzed: 4231</td>
<td>Loss to followup: NR</td>
<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473)</td>
<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Falls at 24 months: 24.5% (26/106) vs. 21.0% (104/496) vs. 13.1% (69/526) vs. 15.8% (98/620) vs. 11.5% (78/676) vs. 10.4% (152/1467)</td>
<td>Falls at 24 months: 24.5% (26/106) vs. 21.0% (104/496) vs. 13.1% (69/526) vs. 15.8% (98/620) vs. 11.5% (78/676) vs. 10.4% (152/1467)</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Falls at 36 months: 22.9% (25/109) vs. 16.2% (76/468) vs. 13.5% (75/557) vs. 14.9% (93/624) vs. 10.8% (163/1509)</td>
<td>Falls at 36 months: 22.9% (25/109) vs. 16.2% (76/468) vs. 13.5% (75/557) vs. 14.9% (93/624) vs. 10.8% (163/1509)</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Falls at 48 months: 19.7% (27/137) vs. 15.6% (70/449) vs. 17.1% (100/584) vs. 12.0% (69/576) vs. 12.3% (189/1532)</td>
<td>Falls at 48 months: 19.7% (27/137) vs. 15.6% (70/449) vs. 17.1% (100/584) vs. 12.0% (69/576) vs. 12.3% (189/1532)</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Recurrent falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473)</td>
<td>Full adjusted analysis, RR (95% CI) of recurrent falls at 12 months</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>A. 1.22 (1.04 to 1.45), p=0.02</td>
<td>A. 1.22 (1.04 to 1.45), p=0.02</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>B. 1.25 (1.10 to 1.41), p&lt;0.0001</td>
<td>B. 1.25 (1.10 to 1.41), p&lt;0.0001</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>C. 1.08 (0.95 to 1.23), p=0.25</td>
<td>C. 1.08 (0.95 to 1.23), p=0.25</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>D. 1.13 (1.00 to 1.28), p=0.05</td>
<td>D. 1.13 (1.00 to 1.28), p=0.05</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>E. 1.13 (0.99 to 1.28), p=0.05</td>
<td>E. 1.13 (0.99 to 1.28), p=0.05</td>
<td>NIH</td>
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<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>F. Reference</td>
<td>F. Reference</td>
<td>NIH</td>
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<tr>
<td>Author, Year</td>
<td>Enrolled Analyzed Loss to Followup</td>
<td>Adjusted Variables for Statistical Analysis</td>
<td>Main Results</td>
<td>Funding Source</td>
<td>Quality</td>
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<tr>
<td>Miller, 2011</td>
<td>Enrolled: 17,310 (11,549 vs. 887 vs. 4874) Analyzed: 17,310 (11,549 vs. 887 vs. 4874) Loss to followup: NR</td>
<td>Models adjusted for the baseline covariates listed in their Table 1</td>
<td>A vs. B vs. C vs. D vs. E vs. F</td>
<td>Government</td>
<td>Fair</td>
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<td></td>
<td>Incidence of fracture events (95% CI) over entire study period: 53 (34 to 79) vs. 128 (118 to 138) vs. 25 (17 to 34) vs. 120 (111 to 130) vs. 53 (20 to 111) vs. 115 (98 to 134) vs. 126 (115 to 138) Incidence of fracture events (95% CI) in the first 15 days of taking medication: 121 (33 to 310) vs. 902 (813 to 998) vs. 90 (55 to 151) vs. 847 (764 to 936) vs. 781 (627 to 961) vs. 890 (790 to 998) Incidence of fracture events (95% CI) after the first 15 days of taking medication: 47 (28 to 53) vs. 46 (39 to 53) vs. 16 (10 to 24) vs. 29 (6 to 86) vs. 49 (37 to 64) vs. 46 (39 to 54)</td>
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<td>HR (95% CI) of fracture event Overall: 2.6 (1.5 to 4.4) vs. 5.1 (3.7 to 7.1) vs. reference vs. 2.2 (0.9 to 5.2) vs. 4.6 (3.2 to 6.6) vs. 5.1 (3.7 to 7.2) First 2 weeks after starting medication: 1.3 (0.4 to 3.8) vs. 8.0 (4.9 to 13.0) vs. NR vs. NR vs. NR vs. NR</td>
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<td></td>
<td>Doses of &lt;75 mg equivalents of codeine/day vs. doses of 76 to 225 mg equivalents of codeine/day: 4.6 (3.2 to 6.6) Doses of &lt;75 mg equivalents of codeine/day vs. doses greater than 225 mg equivalents of codeine/day: 5.1 (3.7 to 7.2) Among high dose opioid users (NSAIDs group as reference): 2.8 (1.6 to 4.7) vs. 6.4 (4.6 to 8.9) Among high dose opioid users A vs. B: 2.1 (1.3 to 3.5)</td>
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<tr>
<td>Saunders, 2010</td>
<td>Enrolled, 2341 Analyzed: 2341 Loss to followup: NR Duration of followup (mean, person-months) (SD): 32.7 (21.3)</td>
<td>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.</td>
<td>Fracture rate: 5.0%/year Adjusted HRs (95% CI) for risk of fracture A. 1 (reference) B. 1.20 (0.92 to 1.56) C. 1.34 (0.89 to 2.01) D. 2.00 (1.24 to 3.24) E. 1.28 (0.99 to 1.64)</td>
<td>National Institute of Drug Abuse</td>
<td>Fair</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; HR=hazard ratio; HRT=hormone replacement therapy; NIH=National Institutes of Health; NSAID=nonsteroidal antiinflammatory drug; NR=not reported; RR=risk ratio; PS=propensity score; VA=Veterans Administration; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Screened Eligible</th>
<th>Enrolled Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carman, 2011</td>
<td>Retrospective cohort United States</td>
<td>Claim submitted for dispensing of opioids or COX-2 inhibitors for ≥180 days from July 2002 to December 2005, patients aged ≥18 years; controls from general populations matched on age, sex, and cohort entry date Exclude: History of MI or revascularization, cancer</td>
<td>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 &lt;1350 mg MED per 90 days 2. 1350 to &lt;2700 mg MED per 90 days 3. 2700 to &lt;8100 mg MED per 90 days 4. 8100 to &lt;18,000 mg MED per 90 days 5. ≥18,000 mg MED per 90 days</td>
<td>A vs. B vs. C vs. D vs. E Age 18 to 29 years: 4.7% vs. 1.2% vs. 0.8% vs. 1.2% vs. 4.7% Age 30 to 39 years: 16.3% vs. 5.4% vs. 4.1% vs. 5.3% vs. 16.3% Age 40 to 49 years: 33.9% vs. 20.7% vs. 17.6% vs. 20.1% vs. 33.9% Age 50 to 64 years: 36.7% vs. 56.0% vs. 56.3% vs. 56.5% vs. 36.7% Age ≥ 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</td>
<td>All relevant claims in database during study period</td>
<td>Screened: NR Eligible, enrolled, analyzed: 426,124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li, 2013</td>
<td>Case-control U.K. General Practice Research Database</td>
<td>Cases (n=11,693): Age 18 to 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 transplant, arrhythmias, treated hypertension, diabetes, ETOH/drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index.</td>
<td>A. Non-use B. Current (0 to 30 days from index) C. Recent (31 to 365 days out) D. Past Use (366 to 730 days out) Cumulative use (number of prescriptions): 1. 1 to 2 2. 3 to 10 3. 11 to 50 4. &gt;50</td>
<td>Mean age (years): 61.8 vs. 61.6 Female sex: 31.1% vs. 31.3% Low BMI (&lt;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% Current smoker: 38.6% vs. 23.3%</td>
<td>Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI)</td>
<td>Screened: 1,700,000 Eligible: Not reported Enrolled: 11,693 cases and 44,897 controls Analyzed: 11,693 cases and 44,897 controls</td>
<td></td>
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</tr>
</tbody>
</table>
Abbreviations: U.K.=United Kingdom; MED=morphine equivalent dose; MI=myocardial infarction; vs.=versus.
See Appendix C. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Carman, 2011 | Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, cardiovascular and other comorbidities, and use of concomitant medications | Adjusted incidence rate of MI, incidence rate ratio  
A. 5.93 (95% CI, 5.58 to 6.30); IRR 2.66 (95% CI, 2.30 to 3.08)  
B. 3.54 (95% CI, 3.11 to 4.01); IRR 1.94 (95% CI, 1.65 to 2.29)  
C. 3.53 (95% CI, 3.15 to 3.94); IRR 1.79 (95% CI, 1.53 to 2.10)  
D. 3.40 (95% CI, 2.76 to 4.14); IRR 1.74 (95% CI, 1.41 to 2.16)  
E. 1.58 (95% CI, 1.40 to 1.78); IRR 1 (reference)  
Adjusted incidence rates of MI or revascularization, incidence rate ratio  
A. 11.91 (95% CI, 11.40 to 12.43); IRR 2.38 (95% CI, 2.15 to 2.63)  
B. 7.98 (95% CI, 7.33 to 8.67); IRR 1.93 (95% CI, 1.72 to 2.15)  
C. 7.94 (95% CI, 7.36 to 8.54); IRR 1.81 (95% CI, 1.62 to 2.01)  
D. 7.53 (95% CI, 6.56 to 8.60); IRR 1.75 (95% CI, 1.50 to 2.01)  
E. 3.38 (95% CI, 3.12 to 3.67); IRR 1 (reference)  
Dosing  
Compared to a cumulative dose of 0 to 1350 mg MED over 90 days, the IRR for 1350 to <2700 was 1.21 (95% CI, 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95% CI, 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95% CI, 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI, 1.32 to 2.26) | Industry | Fair |
| Li, 2013 | 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 to 1.37)  
C. 1.17 (95% CI, 1.10 to 1.24)  
D. 1.06 (95% CI, 0.98 to 1.14)  
1. 1.10 (95% CI, 1.03 to 1.18)  
2. 1.09 (95% CI, 1.02 to 1.17)  
3. 1.38 (95% CI, 1.28 to 1.49)  
4. 1.25 (95% CI, 1.11 to 1.40) | None disclosed | Good |

Abbreviations: CI=confidence interval; IRR=incidence rate ratio; MED=morphine equivalent dose; mg=milligram; MI=myocardial infarction; OR=odds ratio.  
See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Enrolled Analyzed</th>
</tr>
</thead>
</table>
| Deyo, 2013 | Cross-sectional                        | Ambulatory males aged ≥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)  
C. Patients prescribed analgesics (n=909)  
D. Patients not prescribed analgesics (n=10,418)  
E. Patients prescribed sedatives (n=909)  
F. Patients not prescribed sedatives (n=10,418) | A vs. 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  
Sedative-hypnotic use: 24.4% vs. 15.6%  
Diagnosis of depression: 17.3% vs. 11.3%  
Sedative use: 24.4% vs. 15.6% | Review of medical and pharmacy records                                                                                                                     | Enrolled: 11,327  
Analyzed: 11,327 |
| Richardson, 2018 | Matched cohort                        | Women aged 18 to 55 years, starting a long-term opioid, with a coded noninflammatory potentially painful musculoskeletal condition. | A. Long-term opioid use, defined as ≥90 days  
B. Short-term opioid use                                                                                                           | A vs. B  
Median (IQR) age, years: 43 (35 to 49) vs. 43 (36 to 49)  
Female: 100% vs. 100%  
White: 70.4% vs. 60.8% | Searched databases for relevant codes                                                                                                                     | Enrolled: 44,260  
Analyzed: 44,260 |
| Rubinstein, 2017 | Retrospective cohort                  | Men using opioids daily for non-cancer pain in the 100 days before a testosterone test. Men with cancer, a history of cancer, or endocrine disorders other than stable treated hypothyroidism within the year before the test date were excluded. | A. Androgen deficient (defined as morning serum total testosterone <250 ng/dL)  
B. Not androgen deficient                                                                                                   | A vs B  
Demographics not reported by condition, reported according to specific opioid used.  
Secondary variables:  
Obese: 49.1% vs 50.9%  
Diabetes: 50% vs 50%  
Hypertension: 45.3% vs 54.7%  
Hyperlipidemia: 44.1% vs 55.9%  
Statins: 49% vs 51% | Electronic medical record and administrative databases                                                                                                   | Eligible: 1,585  
Analyzed: 1,159 |

Abbreviations: IQR=interquartile range; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyo, 2013</td>
<td>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</td>
<td>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&lt;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&lt;0.001; OR 1.5, 95% CI, 1.1 to 1.9 Dosing Daily opioid dose of &gt;120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to &lt;20 mg MED/day (OR 1.6, 95% CI, 1.0 to 2.4)</td>
<td>National Institutes of Health/National Center for Research Resources</td>
<td>Fair</td>
</tr>
<tr>
<td>Richardson, 2018</td>
<td>Thyroid conditions, low BMI &lt;18 (as a coded condition), adrenal conditions and obesity (as a coded condition), and BMI (categorized as &lt;25 kg/m², ≥25 kg/m² (overweight) or missing) was recorded at the date closest to the start of follow-up, structural gynecology condition and illegal opioid misuse.</td>
<td>Adjusted HR (95% CI), A vs. B Abnormal menstruation: 1.13 (1.05 to 1.21) Menopause: 1.16 (1.10 to 1.23) Low libido: 1.19 (0.96 to 1.48) Infertility: 0.82 (0.64 to 1.06)</td>
<td>North Staffordshire Primary Care Research Consortium</td>
<td>Fair</td>
</tr>
<tr>
<td>Rubinstein, 2017</td>
<td>Specific opioid, dose, age, obesity, diabetes, hypertension, hyperlipidemia, statin use</td>
<td>Effect of dose (per 10mg MSE), OR (95% CI) Fentanyl: 0.96 (0.88 to 1.03) Hydrocodone: 1.18 (1.09 to 1.28) Hydromorphone: 1.34 (0.61 to 2.94) Methadone: 0.99 (0.97 to 1.02) Morphine: 1.05 (0.99 to 1.11) Oxycodone: 1.01 (1.00 to 1.02)</td>
<td>Kaiser Permanente Northern California Community Benefit program</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; HR=hazard ratio; MED=morphine equivalent dose; MSE=morphine standardized equivalent dose; OR=odds ratio; vs.=versus. See Appendix F. Included Studies for full citations
### Table H-14. Key Question 2a: Study of Long-term Opioid Use and Motor Vehicle Accidents – study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Sampling Strategy</th>
<th>Screened Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
</table>
| Gomes, 2013  | Case-control            | Residents aged 15 to 64 with public drug coverage and an opioid prescription (excluding methadone (2003 to 2011) ≥6 months of continuous eligibility for public drug coverage before their index date and ≥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 | Cases vs. Controls  
Mean age (years): 45.76 vs. 45.75  
Female sex: 48.6% vs. 48.3%  
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  
Charlson score  
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. | Screened population: 549,878  
Eligible Cases: 5,300  
Eligible Controls: 43,736  
Controls matched 1:1 |

Abbreviations: ED=emergency room; ICD=international classification of disease; SD=standard deviation; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Gomes, 2013  | 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 (i.e., 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 to 1.21)
C. 1.07 (95% CI, 0.94 to 1.22)
D. 1.08 (95% CI, 0.93 to 1.24)
E. 1.00 (95% CI, 0.88 to 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 to 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 |

Abbreviations: CI=confidence interval; ED=emergency department; ICES=Institute for Clinical Evaluative Sciences; MED=morphine equivalent dose; MOHLTC=Ministry of Health and Long-Term Care; OR=odds ratio.

See Appendix F. Included Studies for full citations.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method for Assessing Outcomes and Confounders</th>
<th>Screened Eligible Enrolled Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scherrer, 2017 Retrospective cohort VHA</td>
<td>18 to 80 years of age, with a diagnosis of depression and free of cancer and HIV, diagnosed with depression. Patients were opioid-free for the 24-month interval prior to the observation period. Incident opioid use could occur at any time prior to onset of treatment-resistant depression. Patients were defined as having TRD if any of the following were recorded in the medical record: a) electroconvulsive therapy, b) MAOI prescription, c) two or more antidepressants (any SSRI, SNRI, TCA or “other” non-MAOI antidepressant) at the same time overlapping by at least 31 days, or d) augmentation therapy (i.e. prescription of a mood stabilizing or atypical antipsychotic after antidepressant treatment).</td>
<td>A. TRD</td>
<td>A vs. B Mean age (years): 48.2 vs. 49.6 Female: 16.4% vs. 12.5% White: 80.1% vs. 76.7% Maximum pain score (0 to 10): 9.3 vs. 8.9</td>
<td>VHA electronic medical record and administrative databases</td>
<td>Eligible: 7,919 Enrolled: 7,919 Analyzed: 6,223</td>
<td></td>
</tr>
<tr>
<td>Scherrer, 2016 Retrospective cohort 3 administrative databases</td>
<td>Opioid naïve prior to study entry, 18 to 80 years of age without depression at start of study and ≥1 visit after followup periods started Excluded patients with cancer</td>
<td>A. 1 to 30 days of opioid use (n=88,610) B. 31 to 90 days of opioid use (n=17,090) C. &gt;90 days of opioid use (n=8055) 1. Opioid dose of 1 to 50 mg/day MED 2. Opioid dose of 51 to 100 mg/day MED 3. Opioid dose of &gt;100 mg/day MED</td>
<td>Characteristics were provided by database Mean age, years: 44.6 to 55.4 Female: 25% White: 68.7% Arthritis: 79.3% Back pain: 64.9% Headache: 24.5% Musculoskeletal pain: 68.0% Neuropathic pain: 28.4% Mean (SD) maximum pain score: 8.4 (2.2) – only provided from VHA database</td>
<td>VHA electronic medical record and administrative databases</td>
<td>Screened: NR Eligible: NR Enrolled: 107,775 Analyzed: 107,775</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MAOI=monoamine oxidase inhibitor; MED=morphine equivalent dose; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; TRD=treatment resistant depression; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations
Table H-17. Key Question 2a: Studies of Long-term Opioid Use and Risk of Depression – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scherrer, 2017</td>
<td>Pain, psychiatric and physical comorbidities, other prescription medication, health care utilization and demographics</td>
<td>Risk of TRD, A vs. B Opioid dose &gt; 50 mg HR 1.07, 95% CI, 0.88 to 1.30</td>
<td>National Institutes of Health</td>
<td>Fair</td>
</tr>
<tr>
<td>Scherrer, 2016</td>
<td>Hazard ratios for time to new-onset depression were estimated using Cox proportional hazards models in which opioid use duration and MED were time-dependent variables. Fully adjusted Cox models included additional, time-dependent control variables for painful conditions and, in the VHA cohort, pain scores to account for change in pain after opioid initiation.</td>
<td>Adjusted HR (95% CI) for new onset depression in VHA and BSWH databases, with multiple models run A. Reference B. 1.18 (1.10 to 1.25) to 1.31 (1.05 to 1.65) C. 1.31 (1.22 to 1.40) to 2.26 (1.63 to 3.14) 1. Reference 2. 0.78 (0.60 to 1.03) to 1.20 (1.10 to 1.31) 3. 0.71 (0.40 to 1.28) to 1.74 (1.49 to 2.04)</td>
<td>National Institutes of Mental Health</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: BSWH=Baylor Scott and White Health; CI=confidence interval; HR=hazard ratio; MED=morphine equivalent dose; TRD=treatment resistant depression; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations
### Table H-18. Key Question 2: Studies of co-prescribing benzodiazepines and Long-term Opioids and Overdose – study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study Setting Duration</th>
<th>Eligibility Criteria</th>
<th>Exposures assessed</th>
<th>Method of Ascertaining and Defining Outcome</th>
<th>Methods to Control Confounding</th>
</tr>
</thead>
</table>
| Dunn, 2015   | Retrospective cohort Integrated managed care system (Group Health Cooperative; Washington) 1997 to 2005 | Adults ≥18 years of age with >1 opioid prescription (none in 6 months prior) and ≥ 3 prescriptions filled in first 90 days and diagnosis of chronic non-cancer pain in 2 weeks prior to first opioid prescription  
  Exclusion: cancer, not enrolled for at least 270 days preceding study entry  
  Followup started on 90th day of episode  
  Individuals censored from followup for disenrollment or end of study | Opioid exposure (MME per day) calculated for continuously updated 90 day exposure window from day 91 of chronic use period  
  Days' supply of sedative hypnotics dispensed (benzodiazepine, barbiturate, muscle relaxants) for 90 day exposure windows as percent of days with coverage | Opioid overdose or adverse event identified from electronic medical records using ICD9 codes  
  Fatal overdoses from Washington vital statistics | Cox proportional hazards model used to estimate risk for overdose conditional on average daily opioid dose (time varying 90-day exposure windows)  
  Baseline covariates: age, sex, tobacco use, diagnosis of depression, SUDs, pain diagnosis, Charlson Index  
  Sedative-hypnotic use assessed as a time-varying covariate |
| Hernandez, 2018 | Retrospective cohort Medicare Part D 2014 | ≥1 opioid prescription in 2014 and continuously enrolled from first opioid claim end of study or death  
  Exclusions: cancer diagnosis in 2013 or 2014 | Time dependent variables:  
  A. Opioid supply only on day before overdose or censoring (reference)  
  B. Opioid and benzodiazepine supply on day before overdose or censoring and history of 1 to 90 days  
  C. Opioid and benzodiazepine supply on day before overdose or censoring and history of 91 to 180 days  
  D. Opioid and benzodiazepine supply on day before overdose or censoring and history of 181 to 270 days  
  E. Opioid and benzodiazepine supply on day before overdose or censoring and history of ≥271 days | Inpatient or outpatient claim with an opioid overdose diagnosis code | Cox proportional hazard models comparing opioid/benzodiazepine exposure variables to opioid only exposure  
  Baseline covariates: age, sex, race, disability, CMS priority chronic conditions including alcohol use disorder, anxiety, depression, drug use disorder, fibromyalgia, pain, PTSD, psychosis, schizophrenia |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study Setting</th>
<th>Duration</th>
<th>Eligibility Criteria</th>
<th>Exposures assessed</th>
<th>Method of Ascertaining and Defining Outcome</th>
<th>Methods to Control Confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun, 2017</td>
<td>Retrospective cohort</td>
<td>Marketscan data (private insurance plans) 2001 to 2013</td>
<td>Continuous enrollment in a plan with medical and pharmacy benefits from 2001 to 2013, aged 18 to 64 years and ≥1 opioid prescription Excluded patients with cancer</td>
<td>≥1 days of concurrent benzodiazepine use in any given calendar year (fill dates and day supply)</td>
<td>Primary outcome: ED or inpatient admission for opioid overdose (ICD9 for opioid poisoning or adverse event - respirator depression) only if occurring within 7 days of an opioid prescription episode (fill date and day supply).</td>
<td>Multivariate logistic regression comparing the association between concurrent benzodiazepine/opioid use and opioid overdose Baseline covariables: age, sex, year, and ICD9 codes for a variety of chronic conditions (e.g. depression, psychosis, drug abuse, alcohol abuse, etc.). Sensitivity analyses: alternative definitions of overlap (25% of opioid days' supply), opioid overdose within 30 days of opioid episode, less restrictive 2 year enrollment criteria.</td>
</tr>
</tbody>
</table>

Abbreviations: ED=emergency department; ICD=international classification of disease; MME=morphine milligram equivalents; PTSD=post-traumatic stress disorder.

See Appendix F. Included Studies for full citations
### Table H-19. Key Question 2: Studies of co-prescribing benzodiazepines and Long-term Opioids and Overdose – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>Population Characteristics</th>
<th>Main Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn, 2015</td>
<td>A. No sedative-hypnotic exposure in 90 days before overdose</td>
<td>n=9940 Mean age: 54 years Female: 60% Tobacco use: 29% Depression: 27% SUDs: 6% Mean Charlson score: 0.71 Pain diagnosis: back 38%, extremity pain 30%, osteoarthritis 13%, injury 12%, neck 9% Any sedative-hypnotic: 75% Any muscle relaxant: 52% Any benzodiazepine: 43% Sedative-hypnotic ≥45 of 90 day episode: 32%</td>
<td>Total opioid exposed: 148 per 100,000 person-years No opioid exposure: 36 per 100,000 person-years (reference) Any opioid use: 256 per 100,000 person-years A vs. B vs. C vs. D vs. E HR (95% CI) for overdose with sedative-hypnotic use A. Reference (no sedative hypnotic) B. 3.4 (1.6 to 7.2) C. 0.9 (0.2 to 4) D. 3.7 (1.6 to 8.9) E. 2.7 (1.2 to 6)</td>
<td>Good</td>
</tr>
<tr>
<td>Hernandez, 2018</td>
<td>A. Opioid use only (n=50,583)</td>
<td>Mean age, years: 68 vs. 71 vs. 66 vs. 64 vs. 60 Female: 63% vs. 72% vs. 70% vs. 72% vs. 64% White: 82% vs. 88% vs. 88% vs. 88% vs. 89% Disability: 38% vs. 32% vs. 43% vs. 51% vs. 63% Pain diagnosis: 76% vs. 65% vs. 65% vs. 65% vs. 64% Depression: 54% vs. 69% vs. 74% vs. 76% vs. 76% Anxiety: 2% vs. 6% vs. 8% vs. 8% vs. 11%</td>
<td>A vs. B vs. C vs. D vs. E Frequency of opioid overdose by days of overlap (unadjusted): 0.33% (166/50,583) vs. 1.64% (59/3,603) vs. 1.09% (32/2,930) vs. 0.47% (19/4,082) vs. 0.14% (14/10,050) Covariate adjusted Cox proportional hazard model (HR, 95% CI): reference vs. 5.1 (3.7 to 7.0) vs. 1.9 (1.3 to 2.8) vs. 0.6 (0.4 to 1.1) vs. 0.2 (0.1 to 0.3)</td>
<td>Fair</td>
</tr>
<tr>
<td>Sun, 2017</td>
<td>A. Benzodiazepine (n=5425)</td>
<td>Only reports demographics for year 1 (2001) cohort (n=58,814) Mean age, years: 44.5 vs. 42.4; p&lt;0.001 Depression: 17% vs. 4.4%; p&lt;0.001 Psychosis: 0.55% vs. 0.13%; p&lt;0.001 Drug abuse: 1.2% vs. 0.22%; p&lt;0.001 Alcohol abuse: 1.1% vs. 0.3%; p&lt;0.001 MI: 0.41% vs. 0.13%; p&lt;0.001 Dementia: 0.28% vs. 0.12%; p&lt;0.001 CVD: 0.65% vs. 0.19%; p&lt;0.001 COPD: 4.7% vs. 2.0%; p&lt;0.001</td>
<td>A vs. B Annual adjusted incidence of opioid overdose: 2.42% vs. 1.16%; adjusted OR 2.14 (95% CI, 2.05 to 2.24); p&lt;0.001 Intermittent opioid users: 1.45% vs. 1.02%; adjusted OR 1.42 (95% CI, 1.33 to 1.51); p&lt;0.001 Chronic opioid users: 5.36% vs. 3.13%; adjusted OR 1.81 (95% CI, 1.67 to 1.96); p&lt;0.001</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; HR=hazard ratio; OR=odds ratio; SUDs=substance use disorders; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>N Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomes, 2017</td>
<td>Case control population-based, publically-funded Ontario</td>
<td>Cases: Patients prescribed at least 1 opioid prescription over the study period: morphine, codeine, oxycodone, meperidine, hydromorphone, fentanyl who died from opioid-related death not homicide or suicide; Up to 4 controls per case matched on age, gender, year of index date, history of CKD, disease risk index; opioids not for cancer pain; residents of Ontario between 1 August 1997 and December 31, 2013</td>
<td>A. Cases (n=1256) B. Controls (n=4619)</td>
<td>A vs. B Mean age, years: 48 vs. 48 Female: 43% vs. 43% Daily opioid dose: &lt;20 MME: 11% vs. 25% 20 to 49 MME: 18% vs. 29% 50 to 99 MME: 16% vs. 15% 100 to 199 MME: 15% vs. 11% ≥200 MME: 40% vs. 21%</td>
<td>Review of claims and other databases</td>
<td>5,875</td>
</tr>
<tr>
<td>Gomes, 2018</td>
<td>Case control population-based, publically-funded Ontario</td>
<td>Cases: Patients prescribed ≥1 opioid prescription over the study period: morphine, codeine, oxycodone, meperidine, hydromorphone, fentanyl who died from opioid-related death not homicide or suicide; Up to 4 controls per case matched on age, gender, year of index date, history of CKD, Charlson Comorbidity Index; opioids not for cancer pain; residents of Ontario and received prescription opioids between 1 August 1997 and 31 December 2016</td>
<td>A. Cases (n=1417) B. Controls (n=5097)</td>
<td>A vs. B Mean age: 48 vs. 49 Female: 44% vs. 45% Daily opioid dose: &lt;20 MME: 13% vs. 25% 20-49 MME: 23% vs. 30% 50-99MME: 20% vs. 18% 100-199 MME: 17% vs. 11% ≥200 MME: 27% vs. 16%</td>
<td>Review of claims and other databases</td>
<td>5,097</td>
</tr>
<tr>
<td>Peckham, 2018</td>
<td>Retrospective cohort study; commercial claims database</td>
<td>Filled prescription for ≥120 days of treatment for gabapentin and/or 1 opioid; no chronic kidney disease or cancer; 12-month followup</td>
<td>A. Gabapentin only (n=44,152) B. Opioids only (n=736,835) C. Both gabapentin and Opioids (n=15,343)</td>
<td>A vs. B vs. C Mean age, years: 50 vs. 44 vs. 50 Female: 63% vs. 60% vs. 61%</td>
<td>Review of claims database</td>
<td>796,330</td>
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</table>

Abbreviations: CKD=chronic kidney disease; MME=morphine milligram equivalents; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomes, 2017</td>
<td>Opioid dose, age, medication use in prior 120 days (pregabalin, SSRIs, other antidepressants, benzodiazepines, other psychotropic drugs/CNS depressants, methadone, bupronorphine), number of drugs dispensed in past 6 months, receipt of long-acting opioid, alcohol use disorder, Charlson Comorbidity Index, chronic lung disease, diabetes, number of opioid prescribed and number of pharmacies that dispensed opioids for patient in past 6 months.</td>
<td>Coprescription for opioids and gabapentin was associated with increased risk of opioid-related mortality: OR 1.99 (95% CI, 1.61 to 2.47); AOR 1.49 (95% CI, 1.18 to 1.88) vs. opioid prescription alone With high dose gabapentin: OR 2.20 (95% CI, 1.58 to 3.08); AOR 1.58 (95% CI, 1.09 to 2.27) With moderate dose gabapentin: OR 2.05 (95% CI, 1.46 to 2.87); AOR 1.56 (95% CI, 1.06 to 2.28) With low dose gabapentin: OR 1.70 (95% CI, 1.17 to 2.48); AOR 1.32 (95% CI, 0.89 to 1.97)</td>
<td>Government</td>
<td>Fair</td>
</tr>
<tr>
<td>Gomes, 2018</td>
<td>Recent exposure to gabapentin, SSRIs, other antidepressants, benzodiazepines or other CNS depressants, number of medications dispensed in past 6 months, Charlson comorbidity index, number of physicians and pharmacies prescribing and dispensing in past 6 months, receipt of long-acting opioid, opioid dose</td>
<td>Coprescription for opioids and pregabalin was associated with increased risk of opioid-related mortality: OR 1.85 (95% CI, 1.36 to 2.53); AOR 1.68 (95% CI, 1.19 to 2.36) With high dose pregabalin: OR 3.02 (95% CI, 1.58 to 5.77); AOR 2.51 (95% CI, 1.24 to 5.06) With low or moderate dose pregabalin: OR 1.74 (95% CI, 1.22 to 2.49); AOR 1.52 (95% CI, 1.04 to 2.22)</td>
<td>Government</td>
<td>Fair</td>
</tr>
<tr>
<td>Peckham, 2018</td>
<td>Demographic and clinical factors, other benzodiazepines and hypnotics</td>
<td>Reference is to no overuse of gabapentin Drug-related hospitalizations with opioids and gabapentin AOR (95% CI) No overuse: 1.65 (1.46 to 1.85) Mild overuse: 2.66 (2.31 to 3.06) Sustained overuse 1 med: 2.95 (2.46 to 3.54) Sustained overuse both meds: 4.72 (2.67 to 8.37) Drug-related hospitalizations with opioids alone AOR (95% CI) No overuse: 0.69 (0.64 to 0.74) Mild overuse: 1.29 (1.20 to 1.39) Sustained overuse: 1.611 (1.44 to 1.80) Drug-related ED visits with opioids and gabapentin AOR (95% CI) No overuse: 1.50 (1.32 to 1.70) Mild overuse: 1.41 (1.18 to 1.68) Sustained overuse 1 med: 1.26 (0.98 to 1.62) Sustained overuse both meds: 2.73 (1.34 to 5.56) Drug-related hospitalizations with opioids alone AOR (95% CI) No overuse: 1.01 (0.95 to 1.08) Mild overuse: 1.12 (0.1.03 to 1.20) Sustained overuse: 1.10 (0.97 to 1.24)</td>
<td>No funding was used</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: AOR=adjusted odds ratio; CI=confidence interval; OR=odds ratio; SSRI=selective serotonin reuptake inhibitor; vs.=versus.

See Appendix F. Included Studies for full citations

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<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Duration</th>
<th>Setting</th>
<th>Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due to Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamison, 1998</td>
<td>RCT</td>
<td>16 weeks</td>
<td>Single center</td>
<td>Pain clinic United States</td>
<td>Chronic back pain &gt;6 months duration, age 25 to 65 years, average pain intensity &gt;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</td>
<td>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</td>
<td>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</td>
<td>Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36</td>
<td>A vs. B vs. C Average pain (mean, 0 to 100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (mean, 0 to 100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (mean, 0 to 100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (mean): 11.2 vs. 15.0 vs. 31.6 Depression (mean): 10.8 vs. 16.4 vs. 26.9 Irritability (mean): 17.7 vs. 20.5 vs. 33.7 Level of activity (mean, 0 to 100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (mean): 5.9 vs. 5.9 vs. 6.1</td>
<td>A vs. B vs. C Any adverse event: 76% vs. 70% vs. 61% Constipation: 7% vs. 3% vs. 11% Nausea: 54% vs. 42% vs. 33% Vomiting: 18% vs. 12% vs. 7% Pruritus: 4% vs. 2% vs. 7% Dizziness: 7% vs. 7% vs. 7% Somnolence: 9% vs. 7% vs. 0% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Diarrhea: 7% vs. 5% vs. 2% Discontinuation due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 130% (6/54) (p=0.008 for A or C vs. B) Discontinuation due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54)</td>
<td>Industry</td>
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<tr>
<td>Author, Year</td>
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<td>Duration</td>
<td>Setting Country</td>
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<td>Interventions</td>
<td>Sample Characteristics</td>
<td>Screened</td>
<td>Enrolled</td>
<td>Analyzed</td>
<td>Results</td>
<td>Adverse Events and Discontinuation Due to Adverse Events</td>
<td>Funding Source</td>
<td>Quality</td>
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<tr>
<td>Salzman, 1999</td>
<td>RCT</td>
<td>10 days</td>
<td>Multicenter Rheumatology clinics and others United States</td>
<td>18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids</td>
<td>A. Sustained-release Oxycodone (titrated) B. Immediate-release Oxycodone (titrated)</td>
<td>Mean age: 56 years Female: 54% White: 87% Hispanic: 13% Indication: Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions Pain duration: NR</td>
<td>NR</td>
<td>57</td>
<td>57</td>
<td>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)</td>
<td>A vs. B Constipation: 30% (9/30) vs. 37% (10/27) Nausea: 50% (15/30) vs. 33% (9/27) Vomiting: 20% (6/30) vs. 4% (1/27) Pruritus: 30% (9/30) vs. 26% (7/27) Dizziness: 30% (9/30) vs. 22% (6/27) Somnolence: 27% (8/30) vs. 37% (10/27) Postural hypotension: 0% vs. 0% Confusion: 3% (1/30) vs. 0% Dry mouth: 0% vs. 11% (3/27) Nervousness: 0% vs. 7% (2/27) Asthenia: 7% (2/30) vs. 11% (3/27) Headache: 13% (4/30) vs. 26% (7/27) Discontinuation due to adverse events: 20% (6/30) vs. 7% (2/27)</td>
<td></td>
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Abbreviations: NR=not reported; NS=not significant; RCT=randomized controlled trial; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Duration</th>
<th>Setting Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened/Eligible/Randomized/Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler, 2002</td>
<td>RCT</td>
<td>4 weeks</td>
<td>Unclear setting in U.K.</td>
<td>Pain condition: Osteoarthritis Age: ≥18 years Pain severity: Moderate to severe, not otherwise specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Not specified</td>
<td>A. Tramadol 150 to 400 mg taken once daily (SR) B. Tramadol 50 to 100 mg taken TID or QID (IR)</td>
<td>A vs. B Mean age, years: 62.5 vs. 62.6 Female: 54% vs. 63% Race: NR Pain duration: NR, but stated most &gt;5 years</td>
<td>A vs. B Screened: NR Eligible: 279 Randomized: 202 (137 vs. 65) Analyzed: 146 (101 vs. 45)</td>
</tr>
<tr>
<td>Jamison, 1998</td>
<td>RCT</td>
<td>16 weeks</td>
<td>Single center pain clinic in the USA</td>
<td>Pain condition: Chronic back pain Age: 25 to 65 years Pain severity: &gt;40 on 0 to 100 VAS Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: Not specified</td>
<td>A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen</td>
<td>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</td>
<td>Mean age, years: 43 Female: 57% Race: NR Indication: -Failed back syndrome: 39% -Myofascial syndrome: 25% -Degenerative spine disease: 19% -Radiculopathy: 14% -Discogenic back pain: 3% Mean pain duration: 79 months</td>
</tr>
<tr>
<td>Pedersen, 2014</td>
<td>RCT</td>
<td>8 weeks</td>
<td>Single pain center in Norway</td>
<td>Pain condition: Mixed Age: 18 to 75 years Pain severity: Not specified Psychiatric disease: Excluded patients with severe mental disorders Substance use: Excluded Prior opioid use: Required to have prior daily codeine intake between 150 to 300 mg</td>
<td>A. Dihydrocodeine SR 120 to 240 mg/day (dosed 2 to 3 times/day) + paracetamol 2 to 4 g/day (mean NR) B. Dihydrocodeine IR 120 to 240 mg/day (dosed 4 to 6 times/day) + paracetamol 2 to 4 g/day (mean NR)</td>
<td>A vs. B Median (IQR) age, years: 49.0 (42.3 to 56.5) vs. 44.5 (39.0 to 60.0) Female: 61% vs. 47% Median (IQR) BMI: 24.1 (22.2 to 27.7) vs. 29.4 (25.7 to 31.9) Median (IQR) duration of pain, years: 11.5 (8.0 to 18.5) vs. 17.0 (8.8 to 20.0) Median (IQR) duration of opioid use, years: 5.0 (3.0 to 8.0) vs. 10.0 (4.5 to 15.5)</td>
<td>A vs. B Screened: 128 Eligible: NR Randomized: 58 (28 vs. 30) Analyzed: 38 (18 vs. 20)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Duration</td>
<td>Setting Country</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
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<tr>
<td>Steiner, 2011</td>
<td>RCT</td>
<td>12 weeks</td>
<td>75 centers in the USA</td>
<td>Pain condition: Low back pain Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Excluded</td>
<td>A. Buprenorphine 7-day patch 20 mcg/hour B. Buprenorphine 7-day patch 5 mcg/hour C. Oxycodone IR capsules 40 mg/day</td>
<td>A vs. B vs. C Mean (SD) age, years: 50.4 (11.93) vs. 50.2 (12.88) vs. 49.5 (12.37) Female: 46% vs. 52% White: 88% vs. 93% vs. 91% Black: 10% vs. 6% vs. 6% Asian: 0 vs. 1% vs. 0.5% Other race: 2% vs. 0 vs. 2% Mean (SD) weight, kg: 90.24 (21.35) vs. 88.44 (22.61) vs. 90.80 (20.50) Musculoskeletal pain: 93% vs. 93% vs. 88% Neuropathic pain: 7% vs. 7% vs. 11%</td>
<td>A vs. B vs. C Screened: 2066 Eligible: NR Randomized: 662 (219 vs. 222 vs. 221) Analyzed: 660 (219 vs. 221 vs. 220)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index; IQR=interquartile range; IR=immediate release; NR=not reported; QID=four times daily; RCT=randomized controlled trial; SR=sustained release; TID=three times daily; U.K.=United Kingdom; USA=United States of America; VAS=visual analogue scale; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due To Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
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</thead>
</table>
| Adler, 2002 | A vs. B, after treatment | Pain (0 to 100), mean: 21 vs. 22  
Difference from baseline: -26 vs. -29  
Use of escape medication 2 hours after taking study drug: 8% vs. 15%, estimated from graph  
Use of escape medication 3 hours after taking study drug: 16% vs. 4%, estimated from graph | A vs. B  
Constipation: 23% vs. 31%  
Nausea: 36% vs. 36%  
Vomiting: 19% vs. 18%  
Dizziness: 20% vs. 17%  
Headache: 18% vs. 15%  
Drowsiness: 15% vs. 25%  
GI related AEs: 62% vs. 65%  
CNS related AEs: 48% vs. 52%  
Overall discontinuation: 29.9% (41/137) vs. 32.3% (21/65), RR 0.93 (95% CI, 0.60 to 1.43)  
Discontinuation due to AEs: 21.9% (30/137) vs. 15.4% (10/65), RR 1.42 (95% CI, 0.74 to 2.73)  
Discontinuation due to lack of efficacy: 5.8% (8/137) vs. 4.6% (3/62), RR 1.26 (95% CI, 0.35 to 4.61)  
Discontinuation due to AEs and lack of efficacy: 1.4% (2/137) vs. 4.6% (3/65), RR 0.32 (95% CI, 0.05 to 1.85) | Industry | Fair |
| Jamison, 1998 | A vs. B vs. C, after treatment | Average pain (0 to 100), mean (SD): 54.9 (15.87) vs. 59.8 (16.65) vs. 65.5 (19.05)  
Current pain (0 to 100), mean (SD): 51.3 (18.98) vs. 55.3 (20.87) vs. 62.7 (22.81)  
Highest pain (0 to 100), mean (SD): 71.4 (20.93) vs. 75.5 (13.26) vs. 78.9 (19.43)  
Anxiety (0 to 100), mean (SD): 11.2 (16.05) vs. 15.0 (21.89) vs. 31.6 (33.58)  
Depression (0 to 100), mean (SD): 10.8 (17.55) vs. 16.4 (24.50) vs. 26.9 (32.11)  
Irritability (0 to 100), mean (SD): 17.7 (17.27) vs. 20.5 (23.12) vs. 33.7 (34.21)  
Level of activity (0 to 100), mean (SD): 49.3 (49.25) vs. 49.3 (49.33) vs. 51.5 (21.01)  
Hours of sleep per night, mean (SD): 5.9 (2.32) vs. 5.9 (2.05) vs. 6.1 (2.69) | A vs. B, RR (95% CI)  
Constipation: 30% (9/30) vs. 37% (10/27), RR 0.81 (0.39 to 1.69)  
Nausea: 50% (15/30) vs. 33% (9/27), RR 1.50 (0.79 to 2.85)  
Vomiting: 20% (6/30) vs. 15% (4/27), RR 1.35 (0.55 to 3.30)  
Pruritus: 20% (9/30) vs. 22% (6/27), RR 0.92 (0.43 to 2.01)  
Dizziness: 20% (9/30) vs. 22% (6/27), RR 0.92 (0.43 to 2.01)  
Confusion: 2% (1/30) vs. 0%, RR 1.5 (0.1 to 14.9)  
Dry mouth: 0% vs. 7% (2/27), RR 0.17 (0.01 to 1.73)  
Asthenia: 7% (2/30) vs. 11% (3/27), RR 0.67 (0.17 to 2.51)  
Headache: 13% (4/30) vs. 26% (7/27), RR 0.51 (0.17 to 1.56)  
Discontinuation due to AEs: 20% (6/30) vs. 7% (2/27), RR 2.70 (0.59 to 12.26) | Industry | Poor |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due To Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Pedersen, 2014 | A vs. B, at last week of trial participation  
Average pain intensity (0 to 10), median (IQR): 4.93 (3.11 to 6.21) vs. 5.00 (3.29 to 6.14)  
SF-8 PCS (0 to 100), mean (SD): 33.77 (7.36) vs. 37.28 (7.96), p=0.18  
SF-8 MCS (0 to 100), mean (SD): 46.43 (9.87) vs. 43.78 (13.60), p=0.51  
PSQI (0 to 21, higher scores indicate poorer sleep quality), median (IQR): 11.0 (8.0 to 15.0) vs. 8.0 (5.0 to 13.0)  
BDI (0 to 63), median (IQR): 26.0 (24.5 to 37.5) vs. 30.5 (24.5 to 34.75) | A vs. B, RR (95% CI)  
Total AEs: 36 vs. 22  
Constipation: 39.3% (11/28) vs. 26.7% (8/30), RR 1.47 (0.70 to 3.12)  
Nausea: NR vs. 13.3% (4/30)  
Fatigue: 10.7% (3/28) vs. NR  
Headache: 25% (7/28) vs. 10% (3/30), RR 2.50 (0.71 to 8.73)  
Dry mouth: 14.3% (4/28) vs. NR  
Overall discontinuation: 35.7% (10/28) vs. 33.3% (10/30), RR 1.11 (0.55 to 2.25)  
Discontinuation due to lack of efficacy: 14.3% (4/28) vs. 13.3% (4/30), RR 1.07 (0.30 to 3.88)  
Discontinuation due to lack of efficacy and AEs: 10.7% (3/28) vs. 3.3% (1/30), RR 3.21 (0.35 to 29.12)  
Discontinuation due to AEs: 14.3% (4/28) vs. 10% (3/30), RR 1.43 (0.35 to 5.82) | Unclear | Fair |
| Steiner, 2011 | A vs. C  
Pain (0 to 10), difference (SE) vs. B: -0.67 (0.16), p<0.001 vs. -0.75 (0.16), p=0.001  
MOS sleep disturbance subscale, difference (95% CI) vs. B: -6.23 (-9.64 to -2.82) vs. -2.65 (-6.01 to 0.70)  
Oswestry Disability Index, difference (95% CI) vs. B: -1.72 (-3.55 to 0.11) vs. -1.99 (-3.79 to -0.18) | A vs. B vs. C, RR (95% CI) A vs. C  
Any AE: 77% (169/219) vs. 59% (131/221) vs. 73% (160/220), RR 1.06 (0.95 to 1.18)  
SAE: 2% (5/219) vs. 3% (6/221) vs.4% (9/220), RR 0.56 (0.19 to 1.64)  
Constipation: 6% (14/219) vs. 3% (7/221) vs. 6% (14/220), RR 1.00 (0.49 to 2.06)  
Nausea: 12% (27/219) vs. 8% (18/221) vs. 8% (18/220), RR 1.51 (0.85 to 2.65)  
Vomiting NOS: 5% (11/219) vs. 2% (5/221) vs. 4% (9/220), RR 1.23 (0.52 to 2.90)  
Somnolence: 5% (10/219) vs. 2% (4/221) vs. 5% (11/220), RR 0.91 (0.40 to 2.11)  
Death (double-blind phase): 0  
Overall discontinuation: 33% (73/219) vs. 42% (93/221) vs. 28% (61/220), RR 1.20 (0.90 to 1.60)  
Discontinuation due to AE: 13% (29/219) vs. 6% (14/221) vs. 7% (16/220), RR 1.82 (1.02 to 3.25)  
Discontinuation due to AE during run-in period: 13% | Industry | Fair |

Abbreviations: AE=adverse event; BDI=Beck Depression Inventory; CI=confidence interval; CNS=central nervous system; GI=gastrointestinal; MCS=mental component subscale; MOS=Medical Outcomes Study; NOS=not otherwise specified; NR=not reported; PCS=physical component subscale; PSQI= Pittsburgh Sleep Quality Index; RR=risk ratio; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations
### Table H-25. Key Question 3b: Observational studies of short-acting versus long-acting opioids for chronic pain – study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method for Assessing Outcomes and Confounders</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller, 2015</td>
<td>Cohort study, VHA health system databases</td>
<td>Patients with chronic noncancer pain who filled a new opioid analgesic prescription between January 1, 2000, and December 31, 2009.</td>
<td>Mean MED were categorized as 1 mg to &lt;20 mg, 20 mg to &lt;50 mg, 50 mg to &lt;100 mg, and ≥100 mg</td>
<td>Median age: 60 years Female: 6.5% White: 71% Initial mean daily dose: 15 mg</td>
<td>Unintentional overdoses coded as drug or medication poisonings of accidental intent using ICD-9-CM codes (E850.x-860.x) or undetermined intent (E980.x or drug poisoning [960.x-980.x] without an accompanying external cause of injury code). If an e-code indicated that the poisoning was self-inflicted (E950.x) or assault-related (E962.x), it was not counted as an event.</td>
<td>Enrolled: 840,606 Analyzed: 840,606 Loss to followup: none</td>
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</tr>
</tbody>
</table>

Abbreviations: ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; MED=morphine equivalent dose; VHA=Veterans Health Administration.

See Appendix F. Included Studies for full citations

### Table H-26. Key Question 3b: Observational studies of short-acting versus long-acting opioids for chronic pain – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables for Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller, 2015</td>
<td>Age, sex, race, and % service-connected disability (a measure of disability, ranging from 0% to 100%), clinical characteristics(prior falls and fractures, other medical diagnoses, and psychiatric diagnoses), VHA health care utilization (general mental health clinic services, services provided in the PTSD clinic, and use of specific therapies, including intensive therapy, rehabilitation, and substance abuse disorder treatment; emergency department and urgent care visits; and inpatient hospitalizations), and comedication with nonopioid agents (selective cyclooxygenase 2 inhibitors and other NSAIDs).</td>
<td>Overdose risk was greater for patients initiating higher dose therapy, with the risk among those receiving therapy with more than 50 mg equivalents of morphine being at more than twice the risk of overdose events compared with those receiving opioids at 1 to 20 mg equivalents</td>
<td>CDC</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CDC=Centers for Disease Control and Prevention; NSAIDs: nonsteroidal antiinflammatory drugs; PTSD=post-traumatic stress disorder; VHA=Veterans Health Administration.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Duration</th>
<th>Setting Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible Randomized Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afilalo, 2010</td>
<td>RCT 15 weeks</td>
<td>87 sites in the USA, 15 in Canada, 6 in New Zealand, and 4 in Australia</td>
<td>Pain condition: Osteoarthritis of the knee Age: ≥40 years Pain severity: Not specified Psychiatric disease: Excluded patients with unstable psychiatric disease Substance use: Excluded Prior opioid use: Not specified</td>
<td>A. Tapentadol SR 200 to 500 mg/day (mean 350 mg) B. Oxycodone SR 40 to 100 mg/day (mean 70 mg) C. Placebo</td>
<td>Mean (SD) age, years: 58.4 (10.09) vs. 58.2 (10.29) vs. 58.2 (9.15) Female: 62.8% vs. 59.1% vs. 59.3% White: 75.6% vs. 71.6% vs. 79.2% Black: 14.2% vs. 13.2% vs. 11.3% Hispanic: 6.1% vs. 10.8% vs. 5.9% Other race: 4.1% vs. 4.4% vs. 3.6% Mean (SD) BMI: 33.61 (7.967) vs. 34.16 (8.185) vs. 35.08 (9.329) Mean (SD) weight, kg: 94.80 (23.664) vs. 97.43 (24.445) vs. 100.28 (26.720) Severe baseline pain: 85.2% vs. 83.0% vs. 81.8%</td>
<td>A vs. B vs. C Screened: 1578 Eligible: 1030 Randomized: 1030 (346 vs. 345 vs. 339) Analyzed: 1023 (344 vs. 342 vs. 337)</td>
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</tr>
<tr>
<td>Allan, 2001</td>
<td>RCT, crossover 4 weeks</td>
<td>35 centers in Belgium, Canada, Denmark, Finland, U.K., the Netherlands, South Africa</td>
<td>Pain condition: Mixed Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded patients with psychiatric illnesses Substance use: Not specified Prior opioid use: Mixed</td>
<td>A. Fentanyl transdermal titrated from 25 mcg/hour (mean 57.3 mcg/hour) B. Long acting morphine titrated from 60 mg/day (mean 133.1 mg/day)</td>
<td>A vs. B Mean (range) age, years: 50.9 (28 to 82) vs. 51.9 (26 to 82) Female: 47.6% vs. 46.2% White: 99% vs. 97% Neuropathic pain: 25% vs. 27% Other/mixed pain: 51% vs. 49% Both neuropathic and nociceptive pain: 25% vs. 24% Mean (SE) duration of chronic pain, years: 9.5 (0.74) vs. 9.1 (0.73) Morphine or morphine sulfate use before study: 72% vs. 79%</td>
<td>A vs. B Screened: NR Eligible: 256 Randomized: 256 (126 vs. 130) Analyzed: 212</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
<td>Screened Eligible Randomized Analyzed</td>
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<tr>
<td>Allan, 2005</td>
<td>RCT 13 months</td>
<td>Multicenter in Europe</td>
<td>Pain condition: Low back pain Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Not specified</td>
<td>A. Fentanyl transdermal titrated from 25 mcg/hour (mean 57 mcg/hour) B. Morphine SR titrated from 60 mg/day SR morphine (mean 140 mg)</td>
<td>Mean age: 54.0 years Female: 61% Race: NR Nociceptive: 35% Neuropathic: 4% Other/mixed and neuropathic: 46% Other/mixed with psychologic factors: 3% Neuropathic with psychologic factors: 4% Mechanical low back pain: 83% Inflammatory: 8% Trauma/surgery: 39% Metabolic: 1% Other: 3% Mean pain duration: 124.7 months</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 683 (338 vs. 342; 3 group assignment NR)</td>
<td></td>
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<tr>
<td>Baron, 2016 (2 publications)</td>
<td>RCT 12 weeks</td>
<td>Unclear, Germany</td>
<td>Pain condition: Low back pain with neuropathic component Age: ≥18 years Pain severity: ≥6 on 0 to 10 NRS Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Mixed</td>
<td>A. Tapentadol SR 50 to 250 mg BID (mean 379 mg) B. Oxycodone SR/naloxone 10 to 40/5 to 20 mg BID + up to oxycodone SR 10 mg BID (mean 75 mg)</td>
<td>Mean (SD) age, years: 58.1 (11.48) vs. 58.4 (12.23) Female: 59.2% vs. 65.6% White: 100% vs. 100% Mean (SD) BMI: 29.8 (5.55) vs. 29.0 (5.69) Positive painDETECT score: 73.8% vs. 75.8%</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 258 (130 vs. 128) Analyzed: 258 (130 vs. 128)</td>
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</tr>
<tr>
<td>Binsfeld, 2010</td>
<td>RCT 24 weeks</td>
<td>64 sites in Europe</td>
<td>Pain condition: Mixed Age: ≥18 years Pain severity: Moderate to severe, not otherwise specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Mixed</td>
<td>A. Hydromorphone SR 8 to 32 mg QD (mean 18.4 mg) B. Oxycodone SR 20 to 80 mg BID (mean 43.8 mg)</td>
<td>Mean (SD) age, years: 57.1 (13.1) vs. 58.0 (12.8) Female: 55.9% vs. 60.8% Chronic LBP: 57.9% vs. 56.4% Musculoskeletal pain such as osteoarthritis, RA: 22.4% vs. 26.4% Neuropathic pain (postherpetic neuralgia, diabetic polyneuropathies): 10.2% vs. 9.2% Other chronic pain conditions responsive to opioids: 9.4% vs. 8.0% Prior opioid use: 69.7% vs. 71.2%</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 512 Analyzed: 504 (254 vs. 250)</td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Setting Country</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
<td>Screened</td>
<td>Eligible</td>
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</tbody>
</table>
| Buynak, 2010      | RCT          | 85 sites in the USA, 15 in Canada, 3 in Australia | Pain condition: Low back pain  
Age: ≥18 years  
Pain severity: ≥5 on 0 to 10 NRS  
Psychiatric disease: Excluded patients with presence of a clinically significant psychiatric disease  
Substance use: Excluded  
Prior opioid use: Mixed | A. Tapentadol SR 100 to 250 mg BID (mean 313 mg)  
B. Oxycodone SR 20 to 50 mg BID (mean 53 mg)  
C. Placebo | Mean (SD) age, years: 49.4 (13.21) vs. 50.0 (14.21) vs. 50.4 (14.05)  
Age ≥65 years: 12.3% vs. 16.8% vs. 17.2%  
Female: 61.0% vs. 55.2% vs. 57.7%  
White: 72.0% vs. 73.5% vs. 74.3%  
Black: 19.5% vs. 16.8% vs. 15.7%  
Hispanic: 5.7% vs. 6.4% vs. 6.6%  
Other race: 2.8% vs. 3.4% vs. 3.4%  
Mean BMI (SD): 32.09 (9.121) vs. 31.36 (7.449) vs. 31.33 (8.143)  
Mean NRS score (SD): 7.5 (1.33) vs. 7.5 (1.21) vs. 7.6 (1.33)  
Moderate pain intensity: 11.1% vs. 10.2% vs. 13.2%  
Severe pain intensity: 88.9% vs. 89.8% vs. 86.8%  
Prior opioid use: 56.0% vs. 50.3% vs. 53.9% | A vs. B vs. C  
Screened: 1589  
Eligible: 979  
Randomized: 981 (321 vs. 334 vs. 326)  
Analyzed: 965 (318 vs. 328 vs. 319) |
| Hale, 2007 and Gajria, 2008 | RCT          | Unclear, USA                             | Pain condition: Osteoarthritis of the knee or hip  
Age: ≥18 years  
Pain severity: ≥2 on 0 to 3 scale  
Psychiatric disease: Not specified  
Substance use: Not specified  
Prior opioid use: Unclear | A. Hydromorphone SR 8 to 64 mg QD (mean 15.8 mg)  
B. Oxycodone SR 10 to 80 mg BID (mean 24.0 mg) | Mean (SD) age, years: 62.9 (10.32) vs. 64.2 (13.12)  
Female: 76.6% vs. 61.7%  
White: 82.8% vs. 88.3%  
Black: 9.4% vs. 8.3%  
Other race: 7.8% vs. 3.3%  
Mean BMI (SD): 34.2 (8.01) vs. 31.4 (6.34)  
Mean pain intensity (SD): 2.5 (0.50) vs. 2.5 (0.50) | A vs. B  
Screened: NR  
Eligible: NR  
Randomized: 140 (71 vs. 69)  
Analyzed: 124 (64 vs. 60)* |
| Karlsson, 2009     | RCT          | 14 sites in Sweden                       | Pain condition: Osteoarthritis of knee or hip  
Age: >18 years  
Pain severity: ≥4 on 0 to 10 BS-11  
Psychiatric disease: Not specified  
Substance use: Excluded  
Prior opioid use: Mixed | A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean NR)  
B. Tramadol SR tablets 150 to 400 mg/day (mean NR) | Mean (SD) age, years: 64.4 (11.1) vs. 64.2 (9.3)  
Female: 59.4% vs. 53.8%  
White: 98.6% vs. 100%  
Asian: 1.4% vs. 0  
Mean (SD) BS-11 score: 6.16 (1.35) vs. 6.21 (1.55) | A vs. B  
Screened: 172  
Eligible: NR  
Randomized: 135 (69 vs. 66)  
Analyzed: 134 (69 vs. 65) |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened</th>
<th>Eligible</th>
<th>Randomized</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leng, 2015</td>
<td>RCT</td>
<td>6 sites in China</td>
<td>Pain condition: Musculoskeletal pain Age: 18 to 80 years Pain severity: Moderate to severe pain, not otherwise specified Psychiatric disease: Excluded patients with mental disorders Substance use: Excluded Prior opioid use: Unclear</td>
<td>A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean 7.5 mcg/hour) B. Tramadol SR tablets 100 to 400 mg/day (mean 236 mg/hour)</td>
<td>A vs. B Mean (SD) age, years: 57.23 (10.30) vs. 56.77 (11.60) Female: 68.4% vs. 69.9% Mean (SD) weight, kg: 66.70 (10.92) vs. 66.60 (10.89) Intervertebral disk disease: 18.4% vs. 26.3% Spondyloarthritis: 1.5% vs. 0.8% Osteoarthritis: 61.8% vs. 56.4% LBP: 7.4% vs. 9.8% Other reasons for pain: 14.7% vs. 16.5% Mean (SD) duration of pain, weeks: 221.10 (309.77) vs. 194.35 (278.28)</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 280 (141 vs. 139) Analyzed: 269 (136 vs. 133)</td>
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<tr>
<td>Matsumoto, 2005</td>
<td>RCT</td>
<td>Multicenter in the USA</td>
<td>Pain condition: Osteoarthritis of the knee or hip Age: &gt;40 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Not specified</td>
<td>A. Oxymorphone SR 20 mg BID x 2 weeks, then 40 mg BID B. Oxymorphone SR 20 mg BID C. Oxycodone SR 10 mg BID x 2 weeks, then 20 mg BID D. Placebo</td>
<td>A vs. B vs. C vs. D Median age, years: 61 vs. 63 vs. 63 vs. 62 Female: 64% vs. 56% vs. 58% vs. 65% Nonwhite race: 12% vs. 18% vs. 10% vs. 14% Knee osteoarthritis: 78% vs. 77% vs. 75% vs. 75% Duration of osteoarthritis &gt;5 years: 64% vs. 71% vs. 67% vs. 77%</td>
<td>A vs. B vs. C vs. D Screened: NR Eligible: NR Randomized: 491 (121 vs. 121 vs. 125 vs. 124) Analyzed: 489 (121 vs. 119 vs. 125 vs. 124)</td>
<td></td>
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<tr>
<td>Mitra, 2013</td>
<td>RCT</td>
<td>1 site in Townsville, Australia</td>
<td>Pain condition: Mixed Age: &gt;18 years Pain severity: Not specified Psychiatric disease: Excluded patients with comorbid psychiatric history Substance use: Not specified Prior opioid use: Excluded</td>
<td>A. Buprenorphine patch titrated from 5 mcg/hour (mean NR) B. Fentanyl patch titrated from 12.5 mcg/hour (mean NR)</td>
<td>Mean (range) age, years: 49 (22 to 80) Female: 52% Back pain: 61% Other types of pain: 39% Mean duration of pain (range): 11.7 years (6 months to 50 years) Duration of followup: 3 months (35%), 6 months (13%), 12 months (52%)</td>
<td>A vs. B Screened: 82 Eligible: NR Randomized: 46 (22 vs. 24) Analyzed: 30 (14 vs. 16)</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Setting Country</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
<td>Screened</td>
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<tr>
<td>Nicholson, 2006</td>
<td>RCT</td>
<td>5 outpatient pain centers in the USA</td>
<td>Pain condition: Mixed, predominantly non-neuropathic Age: 18 to 85 years Pain severity: ≥4 on 0 to 10 BPI Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Mixed</td>
<td>A. Morphine SR titrated from previous dose (mean 79 mg/day) B. Oxycodone SR titrated from previous dose (mean 85 mg/day)</td>
<td>A vs. B Overall mean (range) age, years: 51.3 (20 to 83) Female: 62.8% vs. 40.7%, p&lt;0.05 Overall white: 93.8% Back pain: 62.8% vs. 51.9% Neck pain: 20.9% vs. 16.7% Arthralgia: 7.0% vs. 14.8% Osteoarthritis NOS: 7.0% vs. 13.0% Pain in limb: 2.3% vs. 18.5%, p=0.021</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 112 (53 vs. 59) Analyzed: 97 (43 vs. 54)</td>
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<td>Niemann, 2000</td>
<td>RCT, crossover</td>
<td>Multicenter in Denmark</td>
<td>Pain condition: Pancreatitis Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Required to be currently treated by opioids</td>
<td>A. Fentanyl transdermal 25 to 100 mcg/hour (mean 55.6 mcg/hour) B. Morphine SR dose range NR (mean 128.3 mg/day)</td>
<td>Median age, years: 47 Female: 33.3% Race: NR Etiology of chronic pancreatitis: -Alcohol abuse: 94.4% -Sjögren's syndrome: 5.6% Median duration of chronic abdominal pain: 9 years</td>
<td>Screened: NR Eligible: NR Randomized: 18 Analyzed: 18</td>
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<td>Rauck, 2006 and 2007</td>
<td>RCT</td>
<td>Multicenter in the USA</td>
<td>Pain condition: Low back pain Age: 30 to 70 years Pain severity: &gt;4 on 0 10 BPI Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Excluded those treated with SR opioid, used SR opioid in last 6 months</td>
<td>A. Morphine SR once daily (mean 64 mg/day) B. Oxycodone SR twice daily (mean 53 mg/day)</td>
<td>A vs. B Median (range) age, years: 50 (28 to 70) Female: 63.5% vs. 58.2% White: 75.9% vs. 82.5% Black: 23.2% vs. 16.9% Other race: 1% vs. 0.5% Median weight, kg: 87 vs. 91 Mechanical cause of back pain: 76.4% vs. 84.7%, p&lt;0.04 Nonmechanical cause of back pain: 23.6% vs. 15.3% Nerve involvement: 36.9% vs. 27%, p&lt;0.04 Median length of back pain, years: 7 vs. 6</td>
<td>A vs. B Screened: NR Eligible: NR Randomized: 392 (203 vs. 189) Analyzed: 266 (132 vs. 134)</td>
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<td>Author, Year</td>
<td>Study Design</td>
<td>Setting Country</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
<td>Screened</td>
<td>Eligible</td>
<td>Randomized</td>
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<tr>
<td>Ueberall, 2015 and 2016</td>
<td>RCT</td>
<td>88 medical centers in Germany</td>
<td>Pain condition: Low back pain&lt;br&gt;Age: ≥18 years&lt;br&gt;Pain severity: Moderate to severe, not otherwise specified&lt;br&gt;Psychiatric disease: Not specified&lt;br&gt;Substance use: Not specified&lt;br&gt;Prior opioid use: Required an around-the-clock therapy with any of the 3 mentioned WHO step III opioids</td>
<td>A. Oxycodone/naloxone SR (mean 113 mg morphine equivalents)&lt;br&gt;B. Oxycodone SR (mean 107 morphine equivalents)&lt;br&gt;C. Morphine SR (mean 108 morphine equivalents)</td>
<td>A vs. B vs. C&lt;br&gt;Mean (SD) age, years: 46.1 (9.9) vs. 46.7 (9.9) vs. 46.5 (9.3)&lt;br&gt;Female: 55.8% vs. 55.3% vs. 56%&lt;br&gt;Mean (SD) BMI: 27.4 (5.0) vs. 27.0 (4.5) vs. 27.3 (5.9)&lt;br&gt;Pain duration &gt;3 to 12 months: 49.8% vs. 50% vs. 52.3%&lt;br&gt;Pain duration &gt;1 year: 30.9% vs. 30% vs. 30.3%&lt;br&gt;Mean (SD) pain intensity: 47.2 (18.9) vs. 46.8 (21.2) vs. 47.7 (21.4)</td>
<td>A vs. B vs. C&lt;br&gt;Screened: 901&lt;br&gt;Eligible: 901&lt;br&gt;Randomized: 901 (301 vs. 300 vs. 300)&lt;br&gt;Analyzed: 901 (301 vs. 300 vs. 300)</td>
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<td>Wild, 2010</td>
<td>RCT</td>
<td>53 sites in North America; 36 sites in Europe</td>
<td>Pain condition: Low back pain or osteoarthritis of the knee or hip&lt;br&gt;Age: ≥18 years&lt;br&gt;Pain severity: ≥4 on 0 to 10 NRS&lt;br&gt;Psychiatric disease: Not specified&lt;br&gt;Substance use: Excluded&lt;br&gt;Prior opioid use: Mixed</td>
<td>A. Tapentadol SR 100 to 250 mg BID (mean 390 mg)&lt;br&gt;B. Oxycodone SR 20 to 50 mg BID (mean 74 mg)</td>
<td>A vs. B&lt;br&gt;Mean (SD) age, years: 56.8 (12.5) vs. 58.1 (11.8)&lt;br&gt;Age &lt;65 years: 72.6% vs. 70%&lt;br&gt;Female: 57.6% vs. 56.1%&lt;br&gt;White: 88.6% vs. 91.0%&lt;br&gt;Black: 6.7% vs. 5.8%&lt;br&gt;Hispanic: 2.9% vs. 1.8%&lt;br&gt;Other: 1.8% vs. 1.3%&lt;br&gt;BMI: 31.7 vs. 31.8&lt;br&gt;Mean pain intensity (SD): 7.6 (1.5) vs 7.6 (1.62)&lt;br&gt;Moderate pain: 10% vs 13%&lt;br&gt;Severe pain: 90% vs 87%&lt;br&gt;No prior opioid use: 47.1% vs 49.8%</td>
<td>A vs. B&lt;br&gt;Screened: 1123&lt;br&gt;Eligible: NR&lt;br&gt;Randomized: 1121&lt;br&gt;Received drug: 1117 (894 vs. 223)</td>
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Abbreviations: BID=twice daily; BMI=body mass index; BPI= Brief Pain Inventory; BS-11=numerical 11 point box; LBP= low back pain; NR= not reported; NRS= numerical rating scale; QD=four times daily; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SR=sustained release; U.K.=United Kingdom; USA=United States of America; vs.=versus; WHO=World Health Organization.

*1 of the investigators, who had enrolled 14 patients at a single site (7 in each treatment group), was issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain by the FDA's Division of Scientific Investigation, these patients are excluded from the analysis in this paper.

See Appendix F. Included Studies for full citations
Table H-28. Key Question 3c: Head-to-head Trials of Different Long-acting Opioids – study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due to Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
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<tr>
<td>Afilalo, 2010</td>
<td>A vs. B vs. C, at 12 weeks</td>
<td>A vs. B vs. C, RR (95% CI) for A vs. B</td>
<td>Industry</td>
<td>Fair</td>
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<td>Average pain intensity, ≥30% reduction: 43.0% (148/344) vs. 24.9% (85/342) vs. 35.9% (121/337), RR 1.73 (95% CI, 1.39 to 2.16) for A vs. B</td>
<td>Serious AEs: 1.2% (4/344) vs. 2.9% (10/342) vs. 1.8% (6/337), RR 0.40 (0.13 to 1.26)</td>
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<td>Average pain intensity, ≥50% reduction: 32.0% (110/344) vs. 17.3% (59/342) vs. 24.3% (82/337), RR 1.85 (95% CI, 1.40 to 2.45) for A vs. B</td>
<td>Constipation: 18.9% (148/344) vs. 36.8% (126/342) vs. 6.5% (22/337), RR 1.17 (0.97 to 1.40)</td>
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<td>PGIC of very much improved, much improved, or minimally improved: 79.5% (205/258) vs. 73.5% (147/200) vs. 59.0% (161/273), RR 1.08 (95% CI, 0.97 to 1.20)</td>
<td>Nausea: 21.5% (74/344) vs. 36.5% (125/342) vs. 6.8% (23/337), RR 0.59 (0.46 to 0.75)</td>
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<td>A vs. C, LSMD (95% CI) at week 12</td>
<td>Vomiting: 5.2% (18/344) vs. 17.8% (61/342) vs. 3.3 (11/337), RR 0.29 (0.18 to 0.49)</td>
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<td>Pain (0 to 10 NRS): -0.7 (-1.04 to -0.33)</td>
<td>Pruritus: 7.0% (24/344) vs. 12.6% (43/342) vs. 1.2% (4/337), RR 0.55 (0.34 to 0.89)</td>
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<td>WOMAC, pain subscale: -0.27 (-0.422 to -0.126), p&lt;0.001</td>
<td>Dizziness: 17.7% (61/344) vs. 19.0% (65/342) vs. 4.7% (16/337), RR 0.93 (0.68 to 1.28)</td>
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<td>WOMAC, function subscale: -0.21 (-0.357 to -0.060), p=0.006</td>
<td>Death: 0 vs. 0.3% (1/344) vs. 0, RR 0.33 (0.01 to 8.15)</td>
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<td>EQ-5D: 0.05 (0.02 to 0.09), p=0.004</td>
<td>Mild opioid withdrawal (COWS), 2 to 4 days after end of treatment: 71.1% (6/35) vs. 13.5% (5/37) vs. 0% (0/23), RR 1.27 (0.42 to 3.78)</td>
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<td>SF-36, PCS: 2.8 (1.56 to 3.95), p&lt;0.001</td>
<td>Mild opioid withdrawal (COWS) ≥5 days after end of treatment: 1.4% (1/70) vs. 11.9% (10/84) vs. 8.5% (5/59), RR 0.12 (0.02 to 0.91)</td>
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<td>SF-36, MCS: -1.1 (-2.44 to -0.17)</td>
<td>Moderate opioid withdrawal (COWS) ≥5 days after end of treatment: 0% (0/70) vs. 2.4% (2/84) vs. 0% (0/59), RR 0.24 (0.01 to 4.91)</td>
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<td>B vs. C, LSMD (95% CI) at week 12</td>
<td>SOWS: no statistically significant differences in LSM SOWSs total scores for A vs. C</td>
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<td>Pain (0 to 10 NRS): -0.3 (-0.68 to 0.02)</td>
<td>Discontinued due to AEs: 42.7% (147/344) vs. 64.6% (221/342) vs. 58.6% (130/337), RR 0.66 (0.57 to 0.76)</td>
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<td>WOMAC, pain subscale: -0.17 (-0.338 to 0.000)</td>
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<td>Author, Year</td>
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<td>Adverse Events and Discontinuation Due to Adverse Events</td>
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| Allan, 2001 | A vs. B | Overall AEs: 74% vs. 70%
Pain intensity (0 to 100), mean: 57.8 vs. 62.9, p<0.001
Pain control "good" or "very good": 35% (87/247) vs. 23% (54/234), p=0.002, RR 1.53 (95% CI, 1.14 to 2.04)
SF-36 PCS (0 to 100), mean (95% CI): 28.6 (27.5 to 29.7) vs. 27.4 (26.3 to 28.5), p=0.004
SF-36 MCS (0 to 100), mean (95% CI): 44.4 (42.8 to 46.0) vs. 43.1 (41.5 to 44.8), p=0.030
Patient global efficacy "good" or "very good": 60% vs. 36%, p<0.001
| | A vs. B | "Serious" (not defined): 2.8% vs. 3.8%
Constipation: 16% (41/250) vs. 22% (52/238), RR 0.75 (95% CI, 0.52 to 1.08)
Constipation by bowel function questionnaire:
29% (71/250) vs. 48% (112/238), p<0.001, RR 0.60 (95% CI, 0.47 to 0.77)
Nausea: 26% (64/250) vs. 18% (44/238), RR 1.38 (95% CI, 0.98 to 1.95)
Vomiting: 10% (25/250) vs. 10% (24/238), RR 0.99 (95% CI, 0.58 to 1.69)
Dizziness: 11% (28/250) vs. 4% (9/238), RR 2.96 (95% CI, 1.43 to 6.14)
Somnolence: 18% (45/250) vs. 14% (34/238), RR 1.26 (95% CI, 0.84 to 1.89)
Deaths: None
Discontinuation due to AE (all patients): 11% (27/250) vs. 4% (10/238), RR 2.57 (95% CI, 1.27 to 5.19)
Discontinuation due to AE (patients not previously on fentanyl or morphine): 11% (7/66) vs. 9.8% (6/66), RR 1.17 (95% CI, 0.41 to 3.29) | Funding Source | Industry | Quality |
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<td>Allan, 2005</td>
<td>A vs. B</td>
<td>A vs. B, RR (95% CI)</td>
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<td>Pain intensity (0 to 100 VAS), mean at 56 weeks: 56.0 vs. 55.8</td>
<td>Any AE: 87% vs. 91%</td>
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<td>Severe pain at rest: no differences in ITT analysis (data not provided)</td>
<td>Constipation (ITT): 52% vs. 65% (220/338), RR 0.80 (0.70 to 0.91), p&lt;0.05</td>
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<td>Quality of life (SF-36): no differences between interventions</td>
<td>Nausea: 54% vs. 50%</td>
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<td>Loss of working days: no differences between interventions</td>
<td>Vomiting: 29% vs. 26%</td>
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<td>Pruritus: 15% vs. 20%</td>
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<td>Dizziness: 25% vs. 24%</td>
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<td>Somnolence: 17% vs. 30%</td>
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<td>Fatigue: 17% vs. 14%</td>
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<td>Application site reactions: 9% in transdermal fentanyl group.</td>
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<td>Deaths: None</td>
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<td>Addiction: None reported</td>
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<td>Use of laxatives: 53% (177/336) vs. 66% (221/336), RR 0.80 (0.70 to 0.91), p&lt;0.001</td>
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<td>Use of antiemetics/anticholinergics: 38% vs. 36%</td>
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<td>Use of antihistamines: 21% vs. 12%, p=0.002</td>
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<td>Overall discontinuation: 52% (177/338) vs. 47% (162/342), RR 1.10 (0.95 to 1.29)</td>
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<td>Discontinuation due to AEs: 37% (125/335) vs. 31% (104/337), p=0.098, RR 1.21 (0.98 to 1.49)</td>
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<td>Discontinuation due to lack of efficacy: 5% (18/335) vs. 4% (15/342), RR 1.22 (0.63 to 2.39)</td>
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<td>Author, Year</td>
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<td>Adverse Events and Discontinuation Due to Adverse Events</td>
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<td>Baron, 2016 (2 publications)</td>
<td>A vs. B</td>
<td>Pain (0 to 10 NRS), LS mean change (SEM), week 12: -3.7 (0.25) vs. -2.7 (0.26), p&lt;0.001 for test for non-inferiority and p=0.003 for test for superiority</td>
<td>Industry</td>
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<td>PGIC rating very much or much improved: 54.3% (70/129) vs. 29.6% (37/125), RR 1.83 (95% CI, 1.34 to 2.51)</td>
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<td>painDETECT (0 to 38), LS mean change (SEM): -10.8 (0.67) vs. -7.9 (0.69), p=0.002</td>
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<td>SF-12 PCS (0 to 100) at 12 weeks, mean (SD): 40.5 (9.34) vs. 37.8 (8.84)</td>
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<td>SF-12 MCS (0 to 100) at 12 weeks, mean (SD): 51.1 (11.04) vs. 48.7 (11.57)</td>
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<td>A vs. B, RR (95% CI) ≥1 TEAE: 76.9% (100/130) vs. 83.6% (107/128), RR 0.92 (0.81 to 1.04)</td>
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<td>Serious TEAE: 2.3% (3/130) vs. 1.6% (2/128), RR 1.48 (0.15 to 8.69)</td>
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<td>Constipation: 15.4% (20/130) vs. 25.8% (33/128), RR 0.60 (0.36 to 0.98), p=0.045</td>
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<td>Nausea: 22.3% (29/130) vs. 18.0% (23/128), RR 1.24 (0.76 to 2.03)</td>
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<td>Vomiting: 7.7% (10/130) vs. 16.4% (21/128), p=0.045, RR 0.47 (0.23 to 0.96)</td>
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<td>Pruritus: 6.2% (8/130) vs. 8.6% (11/128), RR 0.72 (0.30 to 1.72)</td>
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<td>Dizziness: 18.5% (24/130) vs. 17.2% (22/128), RR 1.07 (0.64 to 1.81)</td>
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<td>Fatigue: 30.0% (39/130) vs. 24.2% (31/128), RR 1.24 (0.83 to 1.85)</td>
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<td>Mean (SD) testosterone concentration in men ≤64 years at final evaluation, nmol/L (n=19 vs. 11): 11.21 (3.678) vs. 8.99 (4.320)</td>
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<td>Men ≤64 years with testosterone levels below normal range at final evaluation: 10.5% (2/19) vs. 45.5% (5/11), RR 0.23 (0.05 to 1.00)</td>
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<td>No TEAE-related patterns of opioid-induced androgen deficiency in men ≤64 years</td>
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<td>Overall discontinuation: 33.8% (44/130) vs. 62.5% (80/128), RR 0.54 (0.41 to 0.71)</td>
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<td>Discontinuation due to AEs: 21.5% (28/130) vs. 42.2% (54/128), p&lt;0.001, RR 0.51 (0.35 to 0.75)</td>
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<td>-Discontinuation due to GI AEs: 14.6% (19/130) vs. 21.1% (27/128), RR 0.69 (0.41 to 1.18)</td>
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<td>-Discontinuation due to nervous system AEs: 4.6% (6/130) vs. 17.2% (22/128), p=0.001, RR 0.27 (0.11 to 0.64)</td>
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<td>-Discontinuation due to dizziness: 3.1% vs. 12.5%, p=0.005</td>
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<td>-Discontinuation due to skin and subcutaneous tissue AEs: 2.3% vs. 8.6%, p≤0.03</td>
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<td>Author, Year</td>
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<td>Adverse Events and Discontinuation Due to Adverse Events</td>
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<td>Binsfeld, 2010</td>
<td>A vs. B</td>
<td><strong>BPI pain right now (0 to 10), mean difference: -0.12 (95% CI, -0.53 to 0.29)</strong></td>
<td><strong>Total AEs: 81.1% (206/254) vs. 84.8% (212/250), RR 0.96 (0.88 to 1.03)</strong></td>
<td><strong>Industry</strong></td>
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<td><strong>MOS sleep subscale, sleep interference, mean difference: -2.87 (95% CI, -5.94 to 0.19)</strong></td>
<td><strong>SAE: 9.8% (25/254) vs. 8.4% (21/250), RR 1.17 (0.67 to 2.04)</strong></td>
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<td><strong>Constipation: 28.7% (73/254) vs. 26.0% (65/250), RR 1.10 (0.83 to 1.47)</strong></td>
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<td><strong>Nausea: 26.8% (68/254) vs. 31.6% (79/250), RR 0.85 (0.64 to 1.11)</strong></td>
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<td><strong>Vomiting: 12.6% (32/254) vs. 14.4% (36/250), RR 0.87 (0.56 to 1.36)</strong></td>
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<td><strong>Deaths: NR</strong></td>
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<td><strong>Addiction: NR</strong></td>
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<td><strong>Abuse: NR</strong></td>
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<td><strong>Cognitive changes: NR</strong></td>
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<td><strong>Overall discontinuation: 54.7% (139/254) vs. 56.8% (142/250), RR 0.96 (0.82 to 1.13)</strong></td>
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<td><strong>Discontinuation due to AE: 26.4% (67/254) vs. 25.2% (63/250), RR 1.05 (0.78 to 1.41)</strong></td>
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<td><strong>Discontinuation due to lack of efficacy: 8.7% (22/254) vs. 7.2% (18/250), RR 1.20 (0.66 to 2.19)</strong></td>
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<td>Buynak, 2010</td>
<td>A vs. B vs. C, at 12 weeks</td>
<td>Pain (0 to 10 NRS), mean (SD) change: -2.9 (2.66) vs. -2.9 (2.52) vs. -2.1 (2.33)</td>
<td>A vs. B vs. C, RR (95% CI) for A vs. B</td>
<td>Industry</td>
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<td>Average pain intensity, ≥30% reduction: 39.7% (125/315) vs. 30.4% (99/326) vs. 27.1% (86/317), RR 1.31 (95% CI, 1.06 to 1.62) for A vs. B</td>
<td>Reported ≥1 TEAE: 75.5% (240/318) vs. 84.8% (278/328) vs. 59.6% (190/319), RR 0.89 (0.82 to 0.96)</td>
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<td>Average pain intensity, ≥50% reduction: 27.0% (85/315) vs. 18.9% (60/317), RR 1.16 (95% CI, 0.89 to 1.51) for A vs. B</td>
<td>Serious TEAEs: 2.2% (7/318) vs. 3.4% (11/328) vs. 0.9% (3/319), RR 0.66 (0.26 to 1.67)</td>
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<td>PGIC rating much improved or very much improved: 55.5% (131/236) vs. 60.0% (126/210) vs. 32.7% (80/245), RR 0.93 (95% CI, 0.79 to 1.08)</td>
<td>Constipation: 13.8% (44/318) vs. 26.8% (88/328) vs. 5.0% (16/319), RR 0.52 (0.37 to 0.71)</td>
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<td>Pain (0 to 10 NRS): -0.8 (-1.22 to -0.47), p&lt;0.001</td>
<td>Nausea: 20.1% (64/318) vs. 34.5% (113/328) vs. 9.1% (29/319), RR 0.58 (0.45 to 0.76)</td>
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<td>-Moderate baseline pain intensity: -1.8 (-3.15 to -0.48), p=0.009</td>
<td>Vomiting: 9.1% (29/318) vs. 19.2% (63/328) vs. 1.6% (5/319), RR 0.31 to 0.72</td>
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<td>-Severe baseline pain intensity: -0.8 (-1.23 to -0.41), p&lt;0.001</td>
<td>Pruritus: 7.2% (23/318) vs. 16.8% (55/328) vs. 1.9% (6/319), RR 0.43 (0.27 to 0.68)</td>
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<td>BPI: -0.7 (0.18), p&lt;0.001</td>
<td>Dizziness: 11.9% (38/318) vs. 17.1% (56/328) vs. 5.6% (18/319), RR 0.70 (0.48 to 1.02)</td>
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<td>SF-36 PCS: 2.3 (0.65), p&lt;0.001</td>
<td>Insomnia: 4.1% (13/318) vs. 7.6 (25/328) vs. 2.8 (9/319), RR 0.54 (0.28 to 1.03)</td>
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<td>SF-36 MCS: 0.1 (0.70)</td>
<td>Deaths: 0 vs. 0 vs. 0</td>
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<td>EQ-5D: 0.0 (0.002), p=0.02</td>
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<td>Hale, 2007 and Gajria, 2008</td>
<td>A vs. B, mean (SD): 2.3 (0.95) vs. 2.3 (1.00)</td>
<td>A vs. B, RR (95% CI)</td>
<td>Industry</td>
<td>Fair</td>
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<td>Pain relief (0 to 10), mean (SD): 2.3 (0.95) vs. 2.3 (1.00)</td>
<td>Any AE: 78.9% (56/71) vs. 79.1% (53/67), RR 1.00 (0.84 to 1.18)</td>
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<td>Scrutiny of treatment effectiveness good, very good, or excellent: 67.2% (43/64) vs. 66.7% (40/60), RR 1.01 (95% CI, 0.79 to 1.30)</td>
<td>SAE: 4.2% (3/71) vs. 1.5% (1/67), RR 2.83 (0.30 to 26.55)</td>
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<td>WOAMC total score, mean (SD) change from baseline: -2.0 (1.90) vs. -1.8 (2.14)</td>
<td>Constipation: 29.6% (21/71) vs. 25.4% (17/67), RR 1.17 (0.68 to 2.01)</td>
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<td>WOAMC pain subscale, mean (SD) change from baseline: -2.1 (1.96) vs. -2.0 (2.03)</td>
<td>Nausea: 35.2% (25/71) vs. 29.9% (20/67), RR 1.18 (0.73 to 1.91)</td>
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<td>WOAMC stiffness subscale, mean (SD) change from baseline: -2.2 (2.37) vs. -2.2 (2.72)</td>
<td>Vomiting: 16.9% (12/71) vs. 11.9% (8/67), RR 1.41 (0.62 to 3.25)</td>
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<td>WOAMC physical function subscale, mean (SD) change from baseline: -1.9 (1.99) vs. -1.7 (2.1)</td>
<td>Dizziness (excluding vertigo): 14.1% (10/71) vs. 22.4% (15/67), RR 0.63 (0.30 to 1.30)</td>
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<td>Sleep disruption and daytime sleep: 25.7 (17.82) vs. 35.3 (22.56), p&lt;0.012</td>
<td>Somnolence: 25.4% (18/71) vs. 17.9% (12/67), RR 1.41 (0.74 to 2.71)</td>
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<td>MOS sleep problems index, mean (SD) change from baseline: -13.3 (21.10) vs. -5.2 (22.09), p&lt;0.045</td>
<td>Headache: 5.6% (4/71) vs. 10.4% (7/67), RR 0.54 (0.16 to 1.76)</td>
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<td>Karlsson, 2009</td>
<td>A vs. B, at study completion</td>
<td>A vs. B, RR (95% CI)</td>
<td>Industry</td>
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<td>Pain (0 to 10), LSM change from baseline (95% CI): -2.26 (-2.76 to -1.76) vs. -2.09 (-2.61 to -1.58)</td>
<td>Any AEs: 88.4% vs. 78.5%</td>
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<td>Pain relief (0 to 10), mean (SD): 2.3 (0.95) vs. 2.3 (1.00)</td>
<td>Constipation: 18.8% (21/69) vs. 7.7% (5/65), RR 3.96 (1.58 to 9.87)</td>
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<td>Scrutiny of treatment effectiveness good, very good, or excellent: 53.2% (33/62) vs. 53.2% (33/62), RR 1.22 (0.91 to 1.63), p&lt;0.039</td>
<td>Nausea: 30.4% (21/69) vs. 24.6% (16/65), RR 1.24 (0.71 to 2.15)</td>
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<td>WOAMC total score, mean (SD) change from baseline: -1.9 (1.99) vs. -1.7 (2.1)</td>
<td>Pruritus: 2.9% (2/69) vs. 9.2% (6/65), RR 0.31 (0.06 to 1.50)</td>
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<td>WOAMC pain subscale, mean (SD) change from baseline: -2.2 (2.37) vs. -2.2 (2.72)</td>
<td>Dizziness: 15.9% (11/69) vs. 4.6 (3/65), RR 3.45 (1.01 to 11.83)</td>
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<td>WOAMC stiffness subscale, mean (SD) change from baseline: -2.2 (2.37) vs. -2.2 (2.72)</td>
<td>Fatigue: 13.0% (9/69) vs. 18.5% (12/65), RR 0.71 (0.32 to 1.56)</td>
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<td>WOAMC physical function subscale, mean (SD) change from baseline: -1.9 (1.99) vs. -1.7 (2.1)</td>
<td>Hyperhidrosis: 14.5% (10/69) vs. 6.2% (4/65), RR 2.35 (0.78 to 7.14)</td>
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<td>Sleep disruption and daytime sleep: 25.7 (17.82) vs. 35.3 (22.56), p&lt;0.012</td>
<td>Vertigo: 13.0% (9/69) vs. 1.5% (1/65), RR 8.48 (1.10 to 65.08)</td>
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<td>MOS sleep problems index, mean (SD) change from baseline: -13.3 (21.10) vs. -5.2 (22.09), p&lt;0.045</td>
<td>Headache: 11.6% (8/69) vs. 10.8% (7/65), RR 1.08 (0.41 to 2.80)</td>
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<td>Patient preference for patch over tablet: 70.3% (90/128)</td>
<td>Arthralgia: 5.8% (4/69) vs. 3.1% (2/65), RR 1.88 (0.36 to 9.94)</td>
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<td>WOMAC, EQ-5D: No differences between groups</td>
<td>Application site pruritus: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59)</td>
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<td>WOAMC, EQ-5D: No differences between groups</td>
<td>Edema, peripheral: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59)</td>
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<td>WOAMC, EQ-5D: No differences between groups</td>
<td>Nasopharyngitis: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59)</td>
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<td>WOAMC, EQ-5D: No differences between groups</td>
<td>Overall discontinuation: 20.3% (14/69) vs. 32.3% (21/65), RR 0.63 (0.35 to 1.13)</td>
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<td>WOAMC, EQ-5D: No differences between groups</td>
<td>Discontinuation due to AEs: 14.5% (10/69) vs. 28.8% (19/66), RR 0.50 (0.25 to 1.00)</td>
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<td>Leng, 2015</td>
<td>A vs. B, at study completion Pain (0 to 10 VAS) mean (SD) change from baseline: -3.30 (2.29) vs. -3.75 (2.15) Number of nights waking from pain, mean (SD) improvement from baseline: -0.79 (1.47) vs. -1.06 (1.98) &quot;Good&quot; or &quot;very good&quot; sleep: 68.63% (70/102) vs. 68.57% (72/105), RR 1.00 (0.83 to 1.20)</td>
<td>A vs. B, RR (95% CI) Any AE: 56.74% (80/141) vs. 61.59% (85/139), RR 0.93 (0.76 to 1.13) SAEs: 0 vs. 2.2% (3/139), RR 0.14 (0.01 to 2.70) Constipation: 6.0% (9/141) vs. 7.5% (10/139), RR 0.89 (0.37 to 2.12) Nausea: 21.0% (30/141) vs. 21.7% (30/139), RR 0.98 (0.63 to 1.54) Vomiting: 9.6% (14/141) vs. 10.6% (15/139), RR 0.92 (0.46 to 1.83) Dizziness: 24.0% (34/141) vs. 17.4% (24/139), RR 1.40 (0.87 to 2.23) Somnolence: 6.0% (9/141) vs. 7.5% (10/139), RR 0.89 (0.37 to 2.12) Cutaneous reaction: 5.4% (8/141) vs. 6.2% (9/139), RR 0.88 (0.35 to 2.20) Mild to moderate erythema at patch site: 14.9% (21/141) vs. 13.0% (18/139), RR 1.15 (0.64 to 2.06) Use of antiemetics: 2.8% (4/141) vs. 4.4% (6/139), RR 0.66 (0.19 to 2.28) Use of cathartics: 0.7% (1/141) vs. 2.9% (4/139), RR 0.25 (0.03 to 2.18) Mean (SD) SOWS score: 0.53 (1.18) vs. 0.55 (1.64) Overall discontinuation: 28.4% (40/141) vs. 23.7% (33/139), RR 1.19 (0.80 to 1.78) Discontinuation due to AEs: 20.6% (29/141) vs. 18.0% (25/139), RR 1.14 (0.71 to 1.85) Discontinuation due to lack of efficacy: 0.74% (1/136) vs. 0, RR 3.06 (0.13 to 74.61)</td>
<td>Industry</td>
<td>Good</td>
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<td>Author, Year</td>
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<td>Matsumoto, 2005</td>
<td>A vs. B vs. C vs. D, at week 4 Pain (0 to 100 VAS), mean change (SD) from baseline: -26 (NR) vs. -24 (NR) vs. -22 (NR) vs. -17 (NR) WOMAC Pain (0 to 500), mean change (SD) from baseline: -118 (110) vs. -102 (109) vs. -88 (125) vs. -62 (111) WOMAC Function (0 to 1700), mean change (SD) from baseline: -320 (550) vs. -290 (545) vs. -225 (559) vs. -175 (557) Patient’s global assessment (0 to 100 VAS), mean change (SE) from baseline: -28.6 (3.3) vs. -23.2 (3.2) vs. 25.4 (2.8) vs. -19.5 (2.7) SF-36 PCS (0 to 100), mean change (SE) from baseline: 4.5 (0.9) vs. 3.4 (0.9) vs. 4.0 (0.8) vs. 1.8 (0.7) SF-36 MCS (0 to 100), mean change (SE) from baseline: -0.4 (1.1) vs. 1.5 (1.1) vs. -0.8 (0.9) vs. 2.22 (0.9) Sleep, overall quality (0 to 100, 100=excellent), mean change (SE) from baseline: 18.2 (3.2) vs. 13.8 (3.0) vs. 15.3 (2.5) vs. 7.7 (2.5)</td>
<td>A vs. B vs. C vs. D, RR (95% CI) A vs. C Any AE: 91% vs. 95% vs. 88% vs. 57% Constipation: 32% (39/121) vs. 40% (48/119) vs. 36% (45/125) vs. 11% (14/124), RR 0.89 (0.63 to 1.27) Nausea: 60% (72/121) vs. 61% (73/119) vs. 43% (54/125) vs. 10% (13/124), RR 1.38 (1.07 to 1.77) Vomiting: 34% (4/121) vs. 23% (27/119) vs. 10% (13/125) vs. 2% (2/124), RR 0.32 (0.11 to 0.95) Pruritus: 20% (30/121) vs. 19% (23/119) vs. 8% (10/125) vs. 2% (3/124), RR 3.10 (1.58 to 6.06) Dizziness: 31% (38/121) vs. 29% (34/119) vs. 26% (32/125) vs. 4% (5/124), RR 1.23 (0.82 to 1.83) Somnolence: 31% (38/121) vs. 30% (36/119) vs. 27% (34/125) vs. 5% (6/124), RR 1.15 (0.78 to 1.70) Dry mouth: 12% (14/121) vs. 12% (14/119) vs. 15% (19/125) vs. 0.8% (1/124), RR 0.76 (0.40 to 1.45) Headache: 11% (13/121) vs. 29% (7/119) vs. 26% (23/125) vs. 4% (14/124), RR 0.58 (0.31 to 1.10) Overall discontinuation: 56% (68/121) vs. 48% (58/121) vs. 40% (50/125) vs. 37% (46/124), RR 1.40 (1.08 to 1.83) Discontinuation due to AEs: 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 5% (34/124), RR 1.90 (1.33 to 2.72)</td>
<td>Industry</td>
<td>Fair</td>
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<td>Mitra, 2013</td>
<td>A vs. B Pain reduction ≥3 points (0 to 10): 50% (8/16) vs. 43% (6/14) at 3 months, RR 1.17 (95% CI, 0.53 to 2.54), 8% vs. 8% at 6 months (n/N NR), 11% vs. 11% at 12 months (n/N NR) Depression, Anxiety, and Stress Scale 21 (0 to 126), mean: 50 vs. 58 at 3 months (p=NS), 30 vs. 62 at 6 months (p=0.05), 38 vs. 58 at 12 months (p=NS) Physical Disability Index-7 (0 to 70), mean: 39 vs. 38 at 3 months, 30 vs. 40 at 6 months, 35 vs. 41 at 12 months Score of pain, physical activity, additional rescue medication, additional general practitioner/emergency department visit, sleep quality, mood, and side effects of pain medication (SPAASMS) score (0 to 28), mean: 12 vs. 13 at 3 months, 11 vs. 14 at 6 months, 14 vs. 14 at 12 months</td>
<td>Number patients with local skin reaction at 9 months: 0 vs. 1 (estimated from graph) Side effects scale score at 12 months: ≤1 vs. ≤1 (estimated from graph) Discontinued due to AEs or unsatisfactory relief (not separated by AEs only): 41% (8/22) vs. 37.5% (8/24), RR 1.09 (95% CI, 0.49 to 2.41)</td>
<td>Private Practice Research Fund of Townsville</td>
<td>Poor</td>
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<td>Author, Year</td>
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<tr>
<td>Nicholson, 2006</td>
<td>A vs. B, mean improvement from baseline SF-36 PCS: +2.5 vs. +2.1, p=NS SF-36 MCS: +0.8 vs. +4.2, p for differences between groups NR, but p&lt;0.05 vs. baseline only for sustained-release oxycodone BPI pain intensity: -1.9 vs. -1.4, p=NS BPI sleep Interference scale: -2.6 vs. -1.6, p&lt;0.05 Patient global assessment: +2.6 vs. +1.7, p=NS Use of concomitant medications: 80% vs. 88%, p=NS</td>
<td>A vs. B, RR (95% CI) Any AE: NR Serious AEs: 12 overall Constipation: 26% (13/50) vs. 10% (6/58), RR 2.51 (1.03 to 6.12), p=0.04 Nausea: 14% (7/50) vs. 14% (8/58), RR 1.01 (0.40 to 2.60) Dizziness: 2% (1/50) vs. 5% (3/58), RR 0.77 (0.13 to 4.44) Somnolence: 10% (5/50) vs. 7% (4/58), RR 1.45 (0.41 to 5.11) Fatigue: 4% (2/50) vs. 2% (1/58), RR 2.32 (0.22 to 24.83) Cognitive disorder: 4% (2/50) vs. 2% (1/58), RR 2.32 (0.22 to 24.83) Headache: 4% (2/50) vs. 0%, RR 5.78 (0.28 to 117.72) Edema: 0% vs. 3% (2/58), RR 0.23 (0.01 to 4.71) Sedation: 0% vs. 5% (3/58), RR 0.16 (0.01 to 3.12) Overall discontinuation: 57% (30/53) vs. 51% (30/59), RR 1.11 (0.79 to 1.57) Discontinuation due to AEs: 28% (15/53) vs. 22% (13/59), RR 1.28 (0.67 to 2.44) Discontinuation due to lack of efficacy: 2% (1/53) vs. 7% (4/59), RR 0.28 (0.03 to 2.41)</td>
<td>Industry</td>
<td>Fair</td>
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<tr>
<td>Niemann, 2000</td>
<td>A vs. B Patient preference of &quot;preference&quot; or &quot;strong preference&quot;: 47% (8/17) vs. 41.2% (7/17), RR 1.14 (0.54 to 2.44), p=NS Pain control &quot;good&quot; or &quot;very good&quot; (n=18): 44% (8/18) vs. 33.3% (6/18), RR 1.33 (0.58 to 3.07), p=NS Quality of life: no differences in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores</td>
<td>NR</td>
<td>Industry</td>
<td>Fair</td>
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<tr>
<td>Author, Year</td>
<td>Results</td>
<td>Adverse Events and Discontinuation Due to Adverse Events</td>
<td>Funding Source</td>
<td>Quality</td>
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<tr>
<td>Rauck, 2006 and 2007</td>
<td>A vs. B, mean change from baseline BPI (0 to 10): -3.1 vs. -2.8, p=NR &gt;2 point improvement in BPI: 55% (73/132) vs. 44% (59/134), p=0.03 PSQI: 33% vs. 17%, p=0.006 SF-12 PCS: 23% vs. 19%, p=NS SF-12 MCS: 23% vs. 16%, p=NS Mean demands score on WLQ: 22.1 vs. 20.9</td>
<td>A vs. B, RR (95% CI) SAE: 3% (7/203) vs. 5% (9/189), RR 0.72 (0.27 to 1.90) Constipation: 87% vs. 89% Nausea: 50% vs. 47% Vomiting: 24% vs. 19% Dizziness: 58% vs. 64% Drowsiness: 85% vs. 84% Dry mouth: 82% vs. 76% Itchiness: 65% vs. 57% Drug abuse or diversion: 0% (0/203) vs. 2% (4/189), RR 0.10 (0.00 to 1.91) Overall discontinuation: 46% (93/203) vs. 42% (79/189), RR 1.10 (0.87 to 1.37) Discontinuation due to AEs: 19% (38/203) vs. 14% (27/189), RR 1.31 (0.83 to 2.06) Discontinuation due to lack of efficacy: 5% (10/203) vs. 3% (6/189), RR 1.55 (0.57 to 4.19)</td>
<td>Industry</td>
<td>Fair</td>
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<tr>
<td>Author, Year</td>
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<td>Funding Source</td>
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<td>Joubert et al., 2015</td>
<td>A vs. B vs. C, at end of study&lt;br&gt;Pain intensity (0 to 100), mean (SD): 27.1 (21.3) vs. 28.6 (21.7) vs. 20.0 (20.4)&lt;br&gt;Pain improved ≥50% from baseline: 65.5% (197/301) vs. 50.7% (n/N NR) vs. 43.3% (n/N NR)&lt;br&gt;EQ-5D, mean (SD): 0.79 (0.23) vs. 0.69 (0.28) vs. 0.68 (0.30)&lt;br&gt;EQ-5D index improvement beyond MCID: 70.3% vs. 58.7% vs. 57.7%, p=0.003 A vs. B and p=0.002 A vs. C&lt;br&gt;QLIP inventory (0 to 40, 40=least affected), mean (SD): 30.6 (4.9) vs. 27.5 (5.8) vs. 26.4 (5.9)&lt;br&gt;Adequate sleep duration: 95% vs. 83.3% vs. 83%&lt;br&gt;QLIP improved ≥30% from baseline: 90.7% (273/301) vs. 73.3% (220/300) vs. 67.3% (202/300), RR 1.09 (95% CI, 0.98 to 1.21) B vs. C&lt;br&gt;SF-12 PCS, mean (SD) change from baseline: 10.4 (13.6) vs. 7.9 (15.1) vs. 7.7 (12.1)&lt;br&gt;SF-12 MCS, mean (SD) change from baseline: 5.0 (12.4) vs. 2.5 (10.0) vs. 2.3 (10.8)</td>
<td>A vs. B vs. C, RR (95% CI) of B vs. C&lt;br&gt;Constipation: 29.6% (89/301) vs. 55.3% (166/300) vs. 56.7% (170/300), RR 0.98 (0.85 to 1.12)&lt;br&gt;Nausea: 0.7% (2/301) vs. 3% (9/300) vs. 4.7% (14/300), RR 0.64 (0.28 to 1.46)&lt;br&gt;Dizziness: 1.7% (5/301) vs. 8% (24/300) vs. 9.3% (28/300), RR 0.86 (0.51 to 1.44)&lt;br&gt;Fatigue: 19.6% (59/301) vs. 30% (90/300) vs. 30% (90/300), RR 1.00 (0.78 to 1.28)&lt;br&gt;Lack of appetite: 5.6% (17/301) vs. 11.3% (34/300) vs. 17.3% (52/300), RR 0.48 (0.30 to 0.75)&lt;br&gt;Daytime tiredness: 11.3% (34/301) vs. 18.7% (56/300) vs. 21% (63/300), RR 0.89 (0.64 to 1.23)&lt;br&gt;Lack of drive: 10.3% (31/301) vs. 16.7% (50/300) vs. 19.3% (58/300), RR 0.86 (0.61 to 1.21)&lt;br&gt;Impaired concentration: 12.3% (37/301) vs. 23.7% (71/300) vs. 23.3% (70/300), RR 1.01 (0.76 to 1.35)&lt;br&gt;Gastric complaints: 15.3% (46/301) vs. 23.3% (70/300) vs. 23.7% (71/300), RR 0.98 (0.74 to 1.32)&lt;br&gt;Sleep disturbance: 9.6% (29/301) vs. 22.3% (67/300) vs. 23% (69/300), RR -0.97 (0.72 to 1.30)&lt;br&gt;Feeling down: 10.3% (31/301) vs. 20.7% (62/300) vs. 24.7% (74/300), RR 0.84 (0.62 to 1.13)&lt;br&gt;BFI (0 to 100), mean: 30.0 (26.2) vs. 48.2 (32.3) vs. 53.6 (33.1), p=0.001 for A vs. B and C&lt;br&gt;Overall discontinuation: 25.2% vs. 38.3% vs. 35.5%</td>
<td>Industry</td>
<td>Fair</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Results</td>
<td>Adverse Events and Discontinuation Due to Adverse Events</td>
<td>Funding Source</td>
<td>Quality</td>
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<tr>
<td>Wild, 2010</td>
<td>A vs. B</td>
<td>A vs. B, RR (95% CI) ≥ 1 TEAE: 85.7% (766/894) vs. 90.6% (202/223), RR 0.94 (0.90 to 0.99)</td>
<td>Industry</td>
<td>Fair</td>
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<td>Serious TEAEs: 5.5% (49/894) vs. 4.0% (9/223), RR 1.36 (0.68 to 2.72)</td>
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<td>Constipation: 22.6% (202/894) vs. 38.6% (86/223), RR 0.58 (0.48 to 0.72)</td>
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<td>Nausea: 18.1% (162/894) vs. 33.2% (74/223), RR 0.55 (0.43 to 0.69)</td>
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<td>Vomiting: 7.0% (63/894) vs. 13.5% (30/223), RR 0.52 (0.35 to 0.79)</td>
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<td>Pruritus: 5.4% (48/894) vs. 10.3% (23/223), RR 0.52 (0.32 to 0.84)</td>
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<td>Dizziness: 14.8% (132/894) vs. 19.3% (43/223), RR 0.76 (0.56 to 1.04)</td>
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<td>Deaths: 0 vs. 0</td>
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<td>Relevant AEs on labs, vitals, ECGs: 0 vs. 0</td>
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<td>Mean change (SE) PAC-SYM: 0.3 (0.05) vs. 0.5 (0.14)</td>
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<td>COWS, 5 days post treatment, score &lt;5 (no withdrawal): 88% (145/166) vs. 84% (42/50), RR 1.04 (0.91 to 1.19)</td>
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<td>Mean SOWS at 2-5 days post treatment: 6.9-9.5 vs. 7.5-12.3</td>
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<td>Overall discontinuation: 53.8% vs. 36%</td>
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<td>Discontinuation due to AEs: 22.7% (203/894) vs. 36.8% (82/223), RR 0.62 (0.50 to 0.76)</td>
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</table>

Abbreviations: AE=adverse events; ASA=aspirin; BFI=Bowel Function Index; BPI=Brief Pain Inventory; CI=confidence interval; COWS=Clinical Opiate Withdrawal Scale; EQ-5D=European Quality of Life 5-Dimensions Scale; ITT=intention-to-treat; LS=least squares; LSM=least square means; LSMD=least standard mean difference; MCS=mental component subscale; MOS=Medical Outcomes Study; NR=not reported; NS=not significant; NRS=numerical rating scale; NSAID=nonsteroidal antiinflammatory drug; PCS=physical component subscale; PGIC=Patient Global Impression of Change; QLIP=Quality of Life Impairment by Pain; RR=risk ratio; SAE=serious adverse events; SD=standard deviation; SE=standard error; SEM=standard error mean; TEAE=treatment emergent adverse events; SF-12=short form 12-items; SF-36=short-form 36-items; SPAASMS=S-Score for pain, P-Physical activity levels, A-Additional pain medication, A-Additional Physician/ER Visits, S-Sleep, M-Mood, S-Side effects; SOWS=Subjective Opiate Withdrawal Scale; vs.=versus; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Enrolled Analyzed Loss to Followup</th>
</tr>
</thead>
</table>
| Chung, 2018  | Retrospective cohort Tennessee Medicaid recipients, United States | Age 30 to 74 years who filled prescriptions for transdermal fentanyl, oxycodone CR, or morphine SR between January 1, 1999 and December 31, 2011 | A. Transdermal fentanyl (median 100 mg/day MED) (n=8717)  
B. Oxycodone CR (median 120 mg/day MED) (n=14,118)  
C. Morphine SR (median 90 mg/day MED) (n=27,823) | A vs. B vs. C  
Median (IQR) age, years: 50 (42 to 58) vs. 48 (42 to 56) vs. 48 (42 to 55)  
Female: 67.7% vs. 53.9% vs. 59.6%  
White: 85.3% vs. 85.7% vs. 84.6%  
Back pain: 76.5% vs. 78.2% vs. 80.7%  
Other musculoskeletal pain: 12.9% vs. 11.8% vs. 10.7%  
Other pain: 1.8% vs. 1.4% vs. 1.3% | Proportional hazard regression models used to estimate the HRs | Screened: NR  
Eligible: NR  
Enrolled: 50,658 (8717 vs. 14,118 vs. 27,823)  
Analyzed: 50,658 (8717 vs. 14,118 vs. 27,823)  
Loss to followup: NR |
| Hartung, 2007 | Retrospective cohort Medicaid claims United States | Patients prescribed at least one ≥ 28-day supply of methadone, ER oxycodone, ER morphine, or transdermal fentanyl | A. Methadone (n=974)  
B. ER oxycodone (n=1,866)  
C. Transdermal fentanyl (n=1,546)  
D. ER morphine (n=1,298) | A vs. B vs. C vs. D  
Mean age, years: 70.6 vs. 51.1 vs. 57.4 vs. 58.5  
Female: 74% vs. 63% vs. 65% vs. 65%  
Non-White: 6.1% vs. 10.5% vs. 7.7% vs. 9.6%  
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 | Enrolled: 5,684  
Analyzed: 5,684 |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility Criteria</th>
<th>Comparison Groups</th>
<th>Population Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Enrolled Analyzed Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krebs, 2011 Retrospective cohort VA United States</td>
<td>New prescription for ≥ 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; &lt; 17 or &gt; 100 years of age; missing gender data.</td>
<td>A. Methadone (n=28,554) B. Long-acting morphine sulfate (n=79,938)</td>
<td>A vs. B Mean (SD) age, years : 56 (12) vs. 59 (13) Non-White: 52% vs. 49% 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 disorders: 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% Overall 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 percentile MS: 360 to 7200 mg 99th percentile methadone: 124 to 560 mg</td>
<td>All patients meeting eligibility criteria</td>
<td>Enrolled: 108,492 Analyzed: 98,068 Loss to followup: 3,347 (died); 94,721 (censored)</td>
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<tr>
<td>Author, Year</td>
<td>Type of Study, Setting</td>
<td>Eligibility Criteria</td>
<td>Comparison Groups</td>
<td>Population Characteristics</td>
<td>Method For Assessing Outcomes and Confounders</td>
<td>Enrolled Analyzed Loss to Followup</td>
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<tr>
<td>Ray, 2015</td>
<td>Retrospective cohort</td>
<td>Tennessee Medicaid enrollees</td>
<td>Aged 30 to 70 years, with a filled prescription for methadone or morphine SR (January 1997 to December 2009)</td>
<td>A: Morphine SR B: Methadone</td>
<td>Deaths were classified into 3 subgroups: (1) sudden unexpected deaths consistent with either opioid overdose or life-threatening arrhythmias, (2) other respiratory or cardiovascular deaths for which opioid involvement was possible but less certain, and (3) other deaths, which were less likely to be related to opioid toxic effects. Classification was based on the death certificate–documented underlying cause of death, adjudication of terminal medical records and computerized files with both the terminal medical encounters and death certificate information-</td>
<td>Screened: NR Eligible: NR Enrolled: 38,756 (32,742 vs. 6014)</td>
</tr>
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</table>

Abbreviations: CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CR=controlled release; CVD=cardiovascular disease; ED=emergency department; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; IV=intravenous; LA=long acting; MED=morphine equivalent dose; mg=milligram; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease; SD=standard deviation; SR= sustained release; VA=Veterans Affairs; VISN=Veterans integrated service networks; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Chung, 2018</td>
<td>Adjusted for potential differences among groups using propensity scores that included 145 covariates such as demographic variables, calendar time, opioid indication, use of other opioids, cardiovascular medications and diagnoses, respiratory conditions, musculoskeletal diseases, indicators of frailty, other comorbidities, and medical care utilization</td>
<td>A vs. B vs. C Unintentional opioid overdose: 0.25% (15/5957) person-years vs. 0.21% (30/14,423) person-years vs. 0.34% (77/22,686) person-years All deaths: 1.7% (101/5957) person-years vs. 1.3% (196/14,423) person-years vs. 1.6% (364/22,686) person-years Adjusted HR (95% CI), A vs. C Unintentional opioid overdose: 0.77 (0.44 to 1.34) All deaths: 0.96 (0.77 to 1.21) Adjusted HR (95% CI), C vs. B Unintentional opioid overdose: 1.67 (1.06 to 2.63) All deaths: 1.27 (1.05 to 1.52)</td>
<td>NIH</td>
<td>Fair</td>
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<tr>
<td>Hartung, 2007</td>
<td>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</td>
<td>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</td>
<td>NR</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Krebs, 2011
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

Main Results
All-cause mortality: Unadjusted: 3.4% (3,347/98,068) patients died
Highest mortality within 1st 30 days methadone: 1.2% (334/27,885)
MS: 3.7% (2,597/70,183); 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 to 0.49)
Quintile #2: 0.46 (95% CI, 0.37 to 0.56)
Quintile #3: 0.50 (95% CI, 0.41 to 0.61)
Quintile #4: 0.66 (95% CI, 0.54 to 0.81)
Quintile #5: 0.92 (95% CI, 0.74 to 1.16)
Results robust in validation dataset

Ray, 2015
The relative risk of death between groups defined by study opioid use status, adjusted for patient characteristics, was estimated with the hazard ratio (HR) from a proportional hazards regression model, with study opioid use as a time-dependent covariate. The HRs were adjusted for potential differences between patients currently receiving methadone and morphine SR. Patient characteristics were described by 196 covariates, which included calendar time, demographic factors, opioid indication, use and dose of non study opioids, cardiovascular medications and diagnoses, psychiatric medications and diagnoses, medications for musculoskeletal disorders, respiratory conditions, indicators of frailty, other proarrhythmic medications, other comorbidity, and recent medical care utilization.

HR (95% CI) A vs. B
All deaths: 1.46 (1.17 to 1.83), p<0.001
Sudden unexpected death: 1.47 (1.13 to 1.90), p=0.04
-Opioid overdose only: 2.54 (1.33 to 4.84), p=0.005
-Sudden cardiac death only: 1.12 (0.80 to 1.59), p=0.51
-Both opioid overdose and sudden cardiac death: 2.02 (1.21 to 3.37), p=0.07
Other respiratory/cardiovascular deaths: 1.78 (0.91 to 3.46), p=0.09
Other deaths: 1.26 (0.70 to 2.26), p=0.45

Abbreviations: CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CR=controlled release; CVD=cardiovascular disease; ED=emergency department; ER=extended release; ETOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; IV=intravenous; LA=long acting; MED=morphine equivalent dose; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease; SD=standard deviation; SR=sustained release; VA=Veterans Affairs; VISN=Veterans integrated service networks.

See Appendix F. Included Studies for full citations
Table H-31. Key Question 3: Trial of Opioid Dose Escalation Versus Dose Maintenance or Use of Maximum Dose Ceilings

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible Enrolled Analyzed Loss to Followup</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due to Adverse Events</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naliboff, 2011</td>
<td>RCT 12 months</td>
<td>VA pain clinic USA</td>
<td>USA</td>
<td>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 psychiatric disorder in past 2 years</td>
<td>A. Escalating opioid dose; mean MED 52 mg (n=67) B. Stable opioid dose; mean MED 40 mg (n=73)</td>
<td></td>
<td>Screened: not reported Eligible: 140 Enrolled: 140 Analyzed: 134 Loss to followup: 7% (10/140)</td>
<td>A vs. B</td>
<td>Mean (SD) VAS usual pain at 12 months: 5.6 (1.5) vs. 6.2 (1.5); p=0.11* Usual pain VAS decrease ≥1.5 points: 28% (19/67) vs. 20% (15/73); RR 1.38 (95% CI, 0.76 to 2.49) Mean (SD) VAS pain relief at 12 months: 6.0 (1.7) vs. 5.3 (1.8); p=0.11* Increase in pain relief ≥1.5 points: 29% (19/67) vs. 15% (11/73); RR 1.88 (95% CI, 0.97 to 3.66) Worst pain VAS decrease ≥1.5 points: 14% (9/67) vs. 6% (4/73); RR 2.45 (95% CI, 0.79 to 7.59) Mean (SD) ODI at 12 months: 45.8 (14.8) vs. 45.0 (19.4); p=0.85* ODI decrease ≥10 points: 29% (19/67) vs. 23% (20/73); RR 1.04 (95% CI, 0.61 to 1.76) Use of nonopioid treatments (A. n=64; B. n=70): NSAID: 55% (35/64) vs. 60% (42/70); RR 0.92 (95% CI, 0.68 to 1.22) Muscle relaxant: 15% (10/64) vs. 20% (14/70); RR 0.78 (95% CI, 0.37 to 1.63) Antiseizure: 63% (40/64) vs. 66% (46/70); RR 0.95 (95% CI, 0.74 to 1.23) Antianxiety: 29% (19/64) vs. 34% (24/70); RR 0.87 (95% CI, 0.53 to 1.42) Antidepressants: 71% (45/64) vs. 69% (48/70); RR 1.03 (95% CI, 0.82 to 1.28) Topical: 17% (11/64) vs. 16% (11/70); RR 1.06 (95% CI, 0.49 to 2.28) Injectable: 26% (17/64) vs. 36% (25/70); RR 0.74 (95% CI, 0.44 to 1.24) Physical therapy: 48% (31/64) vs. 63% (44/70); RR 0.77 (95% CI, 0.57 to 1.05)</td>
<td>Department of Veterans Affairs</td>
</tr>
</tbody>
</table>
Abbreviations: ABC=Assessment of Blood Consumption; CHF=chronic heart failure; CI=confidence interval; MED=morphine equivalent dose; NSAID=nonsteroidal antiinflammatory drug; ODI=Oswestry Disability Index; RR=risk ratio; SD=standard deviation; USA=United States of America; VAS=visual analogue scale; vs.=versus.

*p-value calculated based on completers (A: n=34; B: n=32)

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design, Duration</th>
<th>Setting, Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashburn, 2011</td>
<td>RCT, crossover up to 42 days total (2 treatment periods of 10 BTP episodes each within 21 days)</td>
<td>46 centers in the USA</td>
<td>Pain condition: Mixed Age: 18 to 80 years Pain severity: ≤8 on 0 to 10 NRS, with 1 to 4 episodes per day of BTP, each lasting &lt;4 hours Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED</td>
<td>A. Fentanyl buccal tablet B. Oxycodone</td>
<td>Mean (SD) age, years: 48.8 (9.3) Female: 62% White: 92% Black: 5% Other race: 3% Back pain: 57% Osteoarthritis: 11% Neck pain: 8% Fibromyalgia: 9% Traumatic injury: 4% Complex regional pain syndrome: 4% Mean (SD) pain intensity in 24 hours prior to enrollment: 5.1 (1.1)</td>
<td>Screened: 486 Eligible: 360 Enrolled: 323 (titration phase) Analyzed: 320 (safety), 183 (efficacy)</td>
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<tr>
<td>Portenoy, 2007</td>
<td>RCT 3 weeks</td>
<td>16 centers in the USA</td>
<td>Pain condition: Low back pain Age: 18 to 80 years Pain severity: ≤6 on a 0 to 10 NRS, with BTP &lt;4 hours Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED</td>
<td>A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 56% at 800 mcg; 24% at 600 mcg; 15% at 400 mcg; 5% at 200 mcg</td>
<td>NR for randomization groups Mean (SD) age, years: 46.6 (10.21) Female: 55% White: 88% Black: 8% Other race: 4% Primary etiology of low back pain degenerative disc disease: 88% Mean (SD) pain intensity: 5.1 (1.21)</td>
<td>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)</td>
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<tr>
<td>Author, Year</td>
<td>Study Design Duration</td>
<td>Setting Country</td>
<td>Eligibility Criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
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<td>Eligible</td>
<td>Enrolled</td>
<td>Analyzed</td>
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<tr>
<td>Simpson, 2007</td>
<td>RCT, crossover 3 weeks</td>
<td>Multicenter clinic setting not described, in the USA</td>
<td>Pain condition: Neuropathic pain Age: 18 to 80 years Pain severity: &lt;7 on 0 to 10 NRS, 1 to 4 episodes of BTP per day Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED</td>
<td>A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo</td>
<td>Mean (SD) age, years: 48.3 (10.42) Female: 63% White: 92% Black: 8% Other race: 0% Mean (SD) BMI: 32.7 (10.15) Diabetic peripheral neuropathy: 32% Complex regional pain syndrome: 23% Traumatic injury: 19% Idiopathic peripheral neuropathy: 13% Radiculopathy: 6% Postherpetic neuralgia: 4% Other reason for pain: 4% Mean (SD) pain intensity: 5.1 (1.03)</td>
<td>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)</td>
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<tr>
<td>Webster, 2013</td>
<td>RCT, crossover Up to 42 days total (2 treatment periods of 10 BTP episodes each within 21 days)</td>
<td>42 sites in the USA</td>
<td>Pain condition: Mixed Age: 18 to 80 years Pain severity: ≤6 on 0 to 10 NRS, 1 to 4 episodes of BTP per day Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED</td>
<td>A. Fentanyl buccal tablet B. Oxycodone</td>
<td>Mean (SD) age, years: 50.8 (9.9) Female: 58% White: 91% Black: 7% Other race: 2% Mean (SD) pain intensity in 24 hours prior to enrollment: 5.1 (1.0)</td>
<td>Screened: 307 Eligible: NR Enrolled: 213 (titration phase) Analyzed: 211 (safety), 137 (efficacy)</td>
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</table>

Abbreviations: BTP=breakthrough pain; MED=morphine equivalent dose; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations
Table H-33. Key Question 3: Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy – results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due To Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashburn, 2011</td>
<td>A vs. B</td>
<td>Pain intensity (0 to 10) at 15 minutes, mean difference (SD): 0.82 (1.12) vs. 0.60 (0.88), p&lt;0.001</td>
<td>A vs. B, RR (95% CI)</td>
<td>Industry</td>
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<td>Pain intensity (0 to 10) at 30 minutes, mean difference (SD): 1.95 (1.47) vs. 1.60 (1.27), p&lt;0.05</td>
<td>Any AE: 38% (106/281) vs. 31% (88/284); RR 1.22 (0.97 to 1.53)</td>
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<td>Pain relief (0 to 5) at 15 minutes, mean (SD): 0.69 (0.74) vs. 0.53 (0.67), p&lt;0.05</td>
<td>SAE: 2 (in 1 patient) vs. 0</td>
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<td>Pain relief (0 to 5) at 30 minutes, mean (SD): 1.50 (0.83) vs. 1.23 (0.76), p&lt;0.05</td>
<td>Nausea: 9% (26/281) vs. 4% (11/284), RR 2.39 (1.20 to 4.74)</td>
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<td>Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes, p&lt;0.05</td>
<td>Pruritus: 0.7% (2/281) vs. 2% (7/284), RR 0.29 (0.06 to 1.38)</td>
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<td>Meaningful pain relief within 30 minutes: 45% vs. 36% of episodes, p&lt;0.05</td>
<td>Dizziness: 3% (9/281) vs. 0.7% (2/284), RR 4.55 (0.99 to 20.86)</td>
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<td>Any pain relief within 15 minutes: 39% vs. 31% of episodes, p&lt;0.05</td>
<td>Somnolence: 2% (6/281) vs. 2% (5/284), RR 1.21 (0.37 to 3.93)</td>
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<td>Any pain relief within 30 minutes: 71% vs. 66% of episodes, p&lt;0.05</td>
<td>Diarrhea: 2% (6/281) vs. 1% (3/284), RR 2.02 (0.51 to 8.00)</td>
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<td>Discontinued during titration phase due to AEs: 11.3% (36/320)</td>
<td>Headache: 4% (12/281) vs. 3% (8/284), RR 1.52 (0.63 to 3.65)</td>
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<td>Discontinued during titration phase due to lack of efficacy: 7.5% (24/320)</td>
<td>Discontinued during titration phase due to AEs: 1.6% (3/191)</td>
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<td>Discontinued during double-blind phase due to AEs: 1.6% (3/191)</td>
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<tr>
<td>Portenoy, 2007</td>
<td>A vs. B</td>
<td>Sum of pain intensity (0 to 10) differences from 5 to 60 minutes, mean (SE): 8.3 (0.66) vs. 3.6 (0.57), p&lt;0.0001</td>
<td>All data reported only for buccal fentanyl</td>
<td>Industry</td>
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<td>BTP episodes with 'meaningful' pain reduction: 70% (289/413) vs. 30% (63/207), RR 2.30 (95% CI, 1.85 to 2.85), p&lt;0.0001</td>
<td>Serious adverse events: 3% (2/77)</td>
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<td>BTP episodes with ≥33% reduction in pain intensity (0 to 10) after 30 minutes: 42% (172/413) vs. 18% (18/207), RR 4.79 (95% CI, 3.03 to 7.56), p&lt;0.0001</td>
<td>Nausea: 1%</td>
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<td>BTP episodes with ≥50% reduction in pain intensity (0 to 10) after 30 minutes: 30% (122/413) vs. 13% (27/207), RR 2.26 (95% CI, 1.54 to 3.12), p&lt;0.0001</td>
<td>Vomiting: 0%</td>
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<td>BTP episodes with ≥33% reduction in pain intensity (0 to 10) after 120 minutes: 65% (269/413) vs. 28% (57/207), RR 2.36 (1.87 to 2.98), p&lt;0.0001</td>
<td>Dizziness: 4%</td>
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<td>BTP episodes with ≥50% reduction in pain intensity (0 to 10) after 120 minutes: 48% (198/413) vs. 16% (33/207), RR 3.01 (2.16 to 4.18), p&lt;0.0001</td>
<td>Somnolence: 0%</td>
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<td>Dysgeusia: 8%</td>
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<td>Dry mouth: 4%</td>
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<td>Withdrawn due to adverse event: 1% (1/77)</td>
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</tr>
<tr>
<td>Author, Year</td>
<td>Results</td>
<td>Adverse Events and Discontinuation Due To Adverse Events</td>
<td>Funding Source</td>
<td>Quality</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>Simpson, 2007</td>
<td>A vs. B Sum pain intensity (0 to 10) differences from 5 to 60 minutes, mean (SE): 9.63 (0.75) vs. 5.73 (0.71), p&lt;0.001 BTP episodes with 'meaningful' pain reduction: 69% vs. 36%, p&lt;0.0001 BTP episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5%, p&lt;0.0001, p&lt;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)</td>
<td>All data reported only for buccal fentanyl: Nausea: 0% Vomiting: 0% Dizziness: 1% Somnolence: 1% Application site AE: 8% (8/103) during open-label dose titration Discontinued early: 2.5% (2/79) Discontinuation due to AEs during open-label dose titration phase: 12% (12/103) Discontinuation due to AEs during double-blind phase: 2.5% (2/79)</td>
<td>Industry</td>
<td>Good</td>
</tr>
<tr>
<td>Webster, 2013</td>
<td>A vs. B Pain intensity (0 to 10) difference at 15 minutes, mean (SD): 0.88 (1.20) vs. 0.76 (1.13), p&lt;0.001 Pain relief (0 to 10) at 15 minutes: 38% vs. 34%, p&lt;0.05 Meaningful pain relief within 15 minutes: 17% vs. 16%, p=NS Meaningful pain relief within 30 minutes: 46% vs. 38%, p&lt;0.01</td>
<td>A vs. B Any AE: 18% (25/138) vs. 14% (20/142); RR 1.29 (95% CI, 0.75 to 2.20)</td>
<td>Industry</td>
<td>Good</td>
</tr>
</tbody>
</table>

Abbreviations: BTP=breakthrough pain; CI=confidence interval; MED=morphine equivalent dose; NR=not relevant; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations
Table H-34. Key Question 3: Trials of Decreasing Opioid Doses or of Tapering Off Opioids Versus Continuation of Opioids- study characteristics

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
</table>
| Blondell, 2010 | Open-label, RCT 6 months | Setting not describe, USA | Men and women aged ≥18 years with well documented chronic non-cancer pain and self-identified addiction to prescription opioids referred by physicians associated with study site program | Potential participants asked to stop taking all opioid medications evening prior to hospitalization for stabilization; following admission, patients given 4 mg buprenorphine sublingually after withdrawal signs and increased by 2 mg every 2 hours until withdrawal improved. Goal was to reduce pain in 24 to 48 hours on stable dose of buprenorphine/naloxone 2 mg/0.5 mg 3 to 4 times daily.  
A. Steady dose buprenorphine at time of hospital discharge to be continued for entire 6 month followup; patients during first 4 weeks were permitted to increase dose to 16 mg/day; participants could opt out and switch to tapering protocol  
B. Tapering doses of buprenorphine over 4 months, then all opioids to be discontinued for 2 months-permitted to increase starting dose up to 16 mg; also permitted to opt out of tapering protocol and initiate steady dose schedule during the 4 month followup | Mean (SD) age, years: 44 (6.4) vs. 46 (14.6)  
Female: 50%  
White: 92%  
History of alcohol use only: 33%  
History of alcohol and drug abuse: 33%  
Prior SUD treatment: 42% | Screened: 12  
Enrolled: 12  
1 drop out of study  
1 relapsed to illicit drug use and lost to followup |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible</th>
<th>Enrolled</th>
<th>Analyzed</th>
<th>Loss to Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurita, 2018</td>
<td>Open-label, parallel-group RCT</td>
<td>Single center outpatient multidisciplinary pain clinic (International)</td>
<td>Patients on waiting list to pain center aged ≥18 years, ≥7 years schooling, pain duration ≥6 months, treatment with oral opioids ≥3 months, and daily opioid dose ≥60 mg oral MED</td>
<td>Phase 1 (all patients) - Multidisciplinary pain team aimed at stable opioid dose levels and regular and clockwise use of sustained release opioids Phase 2: A. Taper off intervention consisted of reduction of 10% of daily opioid dose every week until discontinuation of opioid treatment for up to 6 months. clonidine for opioid withdrawal symptom management (n=15) B. Maintained on the same treatment from Phase 1 for next 6 months (n=20)</td>
<td>A vs. B Mean (SD) age, years: 56.3 (9.2) vs. 50.6 (14.4) Female: 40% vs. 75%, p=0.04 Race: NR Mean (SD) opioid use duration, years: 9.9 (7.1) vs. 6.6 (4.7) Mean opioid dose, MED/day: 367.4 vs. 220.8 Mean pain duration, years: 15.1 vs. 11.4 Mean years of education: 10.9 vs. 12.0 Mean (SD) BPI pain severity (0 to 10): 5.68 (1.36) vs. 6.26 (1.49) Mean (SD) BPI interference (0 to 10): 6.03 (1.88) vs. 6.60 (2.36) Mean (SD) PODS, opioid problems (0 to 32): 12.72 (10.97) vs. 12.00 (10.47)</td>
<td>Screened: 274 Eligible: NR Enrolled 75 in phase 1 Randomized: 35 Analyzed: 30 (at 4th week) Loss to followup: 5</td>
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<tr>
<td>Sullivan, 2017</td>
<td>RCT</td>
<td>Single center outpatient clinic (United States)</td>
<td>Patients with chronic noncancer pain on opioid recruited through clinician referrals and advertisements who were willing to taper opioid dose by ≥50%</td>
<td>A. 22-week outpatient tapering support including psychiatric consultation and 30 minute weekly visits with physician assistant for motivational interviewing and pain self-management training (n=18) B. Usual management for pain including opioid prescriptions, with no restrictions other than avoiding buprenorphine (n=17)</td>
<td>A vs. B Mean age, years: 54.4 (overall) Female: 67% vs. 77% White: 72% vs. 94% Black: 5.6% vs. 0% Asian: 11% vs. 5.6% Other race/ethnicity: 11% vs. 0% Mean opioid use duration: 10.2 years (overall) Mean opioid dose, MED/day: 207.2 vs. 245.2 Mean pain duration: 13.8 years (overall) College graduate, graduate, or professional school: 44% vs. 29% PHQ-9 score ≥10: 61% vs. 53% Mean (SD) BPI pain severity (0 to 10): 5.68 (1.36) vs. 6.26 (1.49) Mean (SD) BPI interference (0 to 10): 6.03 (1.88) vs. 6.60 (2.36) Mean (SD) PODS, opioid problems (0 to 32): 12.72 (10.97) vs. 12.00 (10.47)</td>
<td>Screened: 144 Eligible: 76 Enrolled: 35 Analyzed: 31 completed 22 week followup</td>
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</table>

Abbreviations: BPI=Brief Pain Inventory; MED=morphine equivalent dose; NR=not reported; PHQ=Patient Health Questionnaire; PODS=Prescribed Opioids Difficulties Scale; RCT=randomized controlled trial; SD=standard deviation; SUD=substance use disorder; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations
### Table H-35. Key Question 3: Trials of Decreasing Opioid Doses or of Tapering Off Opioids Versus Continuation of Opioids - study results

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due to Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondell, 2010</td>
<td>Mean stable dose of buprenorphine: 7.5 mg/day at hospital discharge; 9.8 mg/day at 4 weeks. Study terminated early because none of the 6 participants in tapering dose arm could complete the 6-month protocol. 5 switched to stable dose arm (2 in month 1; 1 in month 2; 1 in month 3; 1 in month 4). 1 was admitted to inpatient unit after relapse after 2nd month (terminated due to ethical reasons). In the stable dose arm, 5 completed 6-month protocol and 1 withdrew due to cost of medication. (0/6 vs. 5/6 completed, p=0.015) At 6 month followup: 10 participants completed 5 and 5; 8 receiving opioid replacement therapy, 6 reported improved pain control and physical functioning.</td>
<td>1 discontinued due to relapse; no other reported events</td>
<td>National Institute on Alcohol Abuse and Alcoholism, Donald W. Reynolds Foundation</td>
<td>Poor</td>
</tr>
<tr>
<td>Kurita, 2018</td>
<td>A vs. B Mean (SD) opioid dose, MED/day: 230.6 (142.6) vs. 345.8 (273.3), p=0.23 at 2 to 3 weeks; 226.6 (144.4) vs. 300.8 (238.5), p=0.446 at 4 to 6 weeks Mean (SD) sleep, minutes: 380 (146) vs. 212 (96), p=0.09 at 2 to 3 weeks; 360 (121) vs. 353 (169), p=0.718 at 4 to 6 weeks Mean (SD) average pain: 6.3 (1.6) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 6.3 (2.0), p=1.0 Mean (SD) pain now: 6.3 (2.2) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 5.1 (2.0), p=0.09 at 4 to 6 weeks Mean (SD) anxiety: 6.9 (3.7) vs. 6.6 (4.3), p=0.65 at 2 to 3 weeks; 6.7 (4.0) vs. 6.3 (3.6), p=0.96 at 4 to 6 weeks Mean (SD) depression: 5.0 (4.7) vs. 5.0 (3.3), p=0.65 at 2 to 3 weeks; 6.4 (4.7) vs. 6.0 (3.7), p=0.856 at 4 to 6 weeks</td>
<td>Not reported</td>
<td>Rigshospitalet, Denmark</td>
<td>Poor</td>
</tr>
<tr>
<td>Author Year</td>
<td>Results</td>
<td>Adverse Events and Discontinuation Due to Adverse Events</td>
<td>Funding Source</td>
<td>Quality</td>
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<tr>
<td>Sullivan, 2017</td>
<td>A vs. B</td>
<td>Discontinuation due to adverse events: 5.6% (1/18) vs. 0% (0/17)</td>
<td>National Institute of Drug Abuse</td>
<td>Fair</td>
</tr>
<tr>
<td>Mean opioid dose, MED/day: 111.9 vs. 169.8 at 22 weeks, adjusted difference -42.95 (95% CI, -92.4 to 6.6); 99.51 vs. 138.2 at 34 weeks, adjusted difference -26.7 (95% CI, -83 to 29.6)</td>
<td>Mean opioid dose, change from baseline: -43% vs. -19% at week 22, adjusted difference -25% (95% CI, -52% to 2%); -62% vs. -31% at 34 weeks, adjusted difference -22% (95% CI, -52% to 8%)</td>
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<tr>
<td>Mean BPI pain severity (0 to 10): 4.72 vs. 5.77 at 22 weeks, adjusted difference -0.68 (95% CI, -2.01 to 0.64); 4.67 vs. 6.16 at 34 weeks, adjusted difference -0.91 (95% CI, -2.30 to 0.48)</td>
<td>Mean BPI interference (0 to 10): 4.55 vs. 6.38 at 22 weeks, adjusted difference -1.39 (95% CI, -2.01 to 0.64); 4.49 vs. 6.05 at 34 weeks, adjusted difference -1.21 (95% CI, -2.43 to 0.02)</td>
<td></td>
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</tr>
<tr>
<td>Mean PODS Opioid Problems (0 to 32): 2.94 vs. 7.53 at 22 weeks, adjusted difference -4.90 (95% CI, -8.40 to -0.80); 3.44 vs. 9.25 at 34 weeks, adjusted difference -4.74 (95% CI, -1.13 to 0.64)</td>
<td>Mean PODS Opioid Concerns (0 to 32): 10.00 vs. 11.47 at 22 weeks, adjusted difference 0.16 (95% CI, -3.74 to 4.06); 10.00 vs. 10.75 at 34 weeks, adjusted difference 1.62 (95% CI, -3.27 to 6.51)</td>
<td></td>
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</tr>
<tr>
<td>Mean Insomnia Severity Index (0 to 28): 12.44 vs. 16.80 at 22 weeks, adjusted difference -4.33 (95% CI, -7.22 to 0.96); 13.38 vs. 15.50 at 34 weeks, adjusted difference -2.12 (95% CI, -5.49 to 3.11)</td>
<td>Mean PHQ-9: 8.88 vs. 11.27 at 22 weeks, adjusted difference -2.21 (95% CI, -6.62 to 2.21); 9.00 vs. 11.13 at 34 weeks, adjusted difference 1.89 (95% CI, -0.23 to 2.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean GAD-7: 5.94 vs. 9.07 at 22 weeks, adjusted difference -2.73 (95% CI, -5.99 to 0.53); 6.00 vs. 8.75 at 34 weeks, adjusted difference -2.39 (95% CI, -5.79 to 1.01)</td>
<td>Mean GAD-7: 5.94 vs. 9.07 at 22 weeks, adjusted difference -2.73 (95% CI, -5.99 to 0.53); 6.00 vs. 8.75 at 34 weeks, adjusted difference -2.39 (95% CI, -5.79 to 1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; GAD=generalized anxiety disorder; MED=morphine equivalent dose; PHQ=Patient Health Questionnaire; PODSSD=Prescription Opioid Difficulties Scale; standard deviation; vs.=versus.

See Appendix F. Included Studies for full citations
Table H-36. Key Question 3. Trials of Different Opioid Tapering Protocols and Strategies study characteristics

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Study Design Duration</th>
<th>Setting Country</th>
<th>Eligibility Criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible Enrolled Analyzed Loss to Followup</th>
</tr>
</thead>
</table>
| Hooten, 2015 | Single blinded placebo controlled pilot trial for 15 days | Interdisciplinary pain clinic, academic medical center, USA | Patients recruited at time of admission to ITP from June 2011 to May 2012 who were ≥21 years, on ≥60 mg/day MED, noncancer chronic pain of >6 months duration | A. Varenicline  
B. Placebo | Both groups were detoxed from opioids using a taper schedule with goal of eliminating opioids at conclusion of ITP. | A vs. B  
Median (IQR) age, years: 49.0 (36.0 to 60) vs. 46.0 (29.0 to 53)  
Female: 14% vs. 36%  
Mean BMI: 24.7 vs. 33.1  
White: 100% vs. 100%  
Mean years of education: 14 vs. 16  
Mean pain duration, years: 7 vs. 5  
Median (IQR) MPI pain severity: 50.6 (45.3 to 55.9) vs. 53.3 (47.9 to 61.2)  
Mean CES-D: 31 (24 to 37) vs. 30 (17 to 25) | Screened: NR  
Eligible: NR  
Randomized: 21 (10 vs. 11)  
Completers: 7 vs. 11 |
| 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 | | | Screened: NR  
Eligible: NR  
Enrolled: 42 (21 vs. 21)  
Analyzed: 42 |
| Mark, 2019 | Retrospective cohort Medicaid beneficiaries, USA | | ≥2 prescription opioid fills on separate days for a total combined supply of ≥15 days, aged 18 to 64 years, have used prescription opioids for ≥90 consecutive days at a daily dose of ≥120 mg MED/day, without a diagnosis of cancer | Cox proportional hazard model used | Mean (SD) age, years: 47 (10)  
Female: 49%  
Used ≥120 mg MED/day for 613 days  
Median days using opioids at high dose: 510  
Primary or secondary substance use disorder: 60%  
Mood disorder: 27%  
Anxiety disorder: 25% | |
Abbreviations: BMI=body mass index; CES-D=Center for Epidemiologic Studies Depression Scale; CVD=cardiovascular disease; IQR=interquartile range; ITP=interdisciplinary treatment program; MED=morphine equivalent dose; MPI=Multidimensional Pain Inventory; NR=not reported; SD=standard deviation; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations
Table H-37. Key Question 3: Trials of Different Opioid Tapering Protocols and Strategies – study results

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due to Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooten, 2015</td>
<td>A vs. B</td>
<td>Median (IQR) duration of opioid taper, days: 18 (14 to 19) vs. 15 (14 to 17)</td>
<td>No adverse events reported in both groups.</td>
<td>Mayo foundation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR) MPI dismissal: 34.6 (24 to 53.3) vs. 41.3 (34.0 to 43.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR) change from baseline MPI: 16.0 (2.7 to 21.3) vs. 12.0 (6.6 to 23.3), between group p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR) CES dismissal: 10.0 (6.0 to 14.0) vs. 12.0 (9.0 to 16.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR) change: 21(10-32) vs. 18(0-28), p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR) value of regression coefficient withdrawal symptoms: -0.116 (-0.248 to 0.025) vs. 0.086 (-0.264 to 0.332), p=0.258</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tennant, 1982</td>
<td>A vs. B</td>
<td>Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mark, 2019</td>
<td>Age, sex, opioid prescription drug use patterns, whether the member was started on medications to treat opioid use disorder after the tapering start date, physical diagnosis, mental health, and substance use disorder diagnosis</td>
<td>86% discontinued filling prescription opioids within 21 days 5% discontinued filling prescription opioids in &gt;90 days 49% had an opioid related adverse event</td>
<td>RTI International</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: IQR=interquartile range; MPI=Multidimensional Pain Inventory; NR=not reported; NS=not significant; RTI=Research Triangle Institute; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Duration</th>
<th>Eligibility Criteria</th>
<th>Population Characteristics</th>
<th>N</th>
<th>Instrument</th>
<th>Method of Administration</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbik, 2006</td>
<td>Prospective cohort</td>
<td>Duration unclear</td>
<td>Chronic pain patients attending 1 of 2 pain clinics</td>
<td>Mean (SD) age, years: 43 (9.6) Female: 33% White: 86%, other races not reported Back pain: 39%</td>
<td>155 (with reference standard, of 397 enrolled)</td>
<td>SOAPP (Version 1)</td>
<td>Self-report</td>
<td>Positive urine screening</td>
</tr>
<tr>
<td>Jones, 2012 (Study 2)</td>
<td>Retrospective cohort</td>
<td>6 months</td>
<td>Consecutive pain clinic patients being evaluated for risk of opioid addiction prior to opioid initiation</td>
<td>Mean (SD) age, years: 48 (13) Female: 56% White: 96%, other races not reported Low back pain: 45% Arthritis or fibromyalgia: 21% Joint pain: 14% Pelvic or abdominal pain: 10% Neck or upper back pain: 7%</td>
<td>263</td>
<td>ORT PMO SOAPP-R Clinician assessment</td>
<td>Self-report; clinician interview</td>
<td>Subsequent opioid discontinuation due to abuse</td>
</tr>
<tr>
<td>Jones, 2013</td>
<td>Cohort, unclear if prospective</td>
<td>6 months</td>
<td>Chronic pain patients referred to a pain clinic</td>
<td>Mean (range) age, years: 50 (22 to 91) Female: 58% Race not reported Back pain: 60% Neck pain: 18%</td>
<td>196</td>
<td>BRI ORT SOAPP-R</td>
<td>Self-report (ORT, SOAPP-R); clinician interview (BRI)</td>
<td>Documentation of aberrant behavior during followup</td>
</tr>
<tr>
<td>Jones, 2014</td>
<td>Prospective cohort</td>
<td>6 months</td>
<td>Chronic pain patients referred to a pain clinic</td>
<td>Mean (range) age, years: NR (19 to 85); 32% 40 to 49 years of age Female: 67% White: 80% Back pain: 44% Neck pain: 26% Headache: 13%</td>
<td>124 (includes 49 patients who did not receive opioids)</td>
<td>BRI ORT SOAPP-R</td>
<td>Self-report (ORT, SOAPP-R); clinician interview (BRI)</td>
<td>Documentation of aberrant behavior during followup</td>
</tr>
<tr>
<td>Jones, 2015</td>
<td>Prospective cohort</td>
<td>6 months</td>
<td>Chronic pain patients referred to a pain clinic</td>
<td>Mean (range) age, years: 55 (21 to 92) Female: 49% White: 96% Back pain: 43% Neck pain: 19% Joint pain: 12% Arm or leg pain: 7% Abdominal pain: 4%</td>
<td>257</td>
<td>BRI ORT SOAPP-R BRQ</td>
<td>Self-report (BRQ, ORT, SOAPP-R); clinician interview (BRI)</td>
<td>Documentation of aberrant behavior during followup</td>
</tr>
<tr>
<td>Moore, 2009</td>
<td>Retrospective cohort</td>
<td>Mean 3.8 months</td>
<td>New adult patients at a pain clinic</td>
<td>Mean (SD) age, years: 44 (11) Female: 60% Race not reported Pain not reported</td>
<td>48</td>
<td>SOAPP (Version 1) DIRE ORT Clinician assessment</td>
<td>Self-report (SOAPP, DIRE, ORT); clinician interview</td>
<td>Subsequent opioid discontinuation due to abuse</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Eligibility Criteria</td>
<td>Population Characteristics</td>
<td>N</td>
<td>Instrument</td>
<td>Method of Administration</td>
<td>Reference Standard</td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Webster, 2005</td>
<td>Prospective cohort 12 months</td>
<td>New chronic pain patients at a pain clinic</td>
<td>Mean (SD) age, years: 44 (13) Female: 58% Race not reported Back pain: 45% Head pain: 18% Neuropathic pain: 16% Musculoskeletal pain: 16% Visceral pain: 5%</td>
<td>185</td>
<td>ORT</td>
<td>Self-report</td>
<td>Documentation of aberrant behavior during followup</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BRI=Brief Risk Interview; BRQ=Brief Risk Questionnaire; DIRE=Diagnosis, Intractability, Risk, Efficacy score; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SD=standard deviation; SOAPP=Screener and Opioid Assessment for Patients with Pain; SOAPP-R=Screener and Opioid Assessment for Patients with Pain-Revised; vs.=versus.

See Appendix F. Included Studies for full citations
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>True Positives (n)</th>
<th>False Positives (n)</th>
<th>True Negatives (n)</th>
<th>False Negatives (n)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
<th>AUROC</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbik, 2006</td>
<td>SOAPP score ≥ 8: 30</td>
<td>SOAPP score ≥ 8: 59</td>
<td>SOAPP score ≥ 8: 37</td>
<td>SOAPP score ≥ 8: 14</td>
<td>SOAPP score ≥ 8: 0.68 (95% CI, 0.52 to 0.81)</td>
<td>SOAPP score ≥ 8: 0.39 (95% CI, 0.29 to 0.49)</td>
<td>SOAPP score ≥ 8: 1.11 (95% CI, 0.86 to 1.43)</td>
<td>SOAPP score ≥ 8: 0.83 (95% CI, 0.52 to 1.31)</td>
<td>Not reported</td>
<td>Fair</td>
</tr>
<tr>
<td>Jones, 2012</td>
<td>ORT score &gt; 4: 19</td>
<td>PMQ score &gt; 30: 41</td>
<td>SOAPP-R score &gt; 30: 134</td>
<td>SOAPP score &gt; 17: 65</td>
<td>Clinician assessment of high-risk: 57</td>
<td>ORT score &gt; 4: 0.20 (95% CI, 0.15 to 0.27)</td>
<td>PMQ score &gt; 30: 0.34 (95% CI, 0.20 to 0.51)</td>
<td>SOAPP-R score &gt; 17: 0.39 (95% CI, 0.26 to 0.54)</td>
<td>Clinician assessment of high-risk: 0.71 (95% CI, 0.54 to 0.84)</td>
<td>ORT score ≥ 4: 0.58 (also reported as 0.48)</td>
</tr>
<tr>
<td>Jones, 2013</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>BRI rating high risk (medium to very high): 0.73</td>
<td>ORT score ≥ 4: 0.56 (also reported as 0.48)</td>
<td>SOAPP-R score &gt; 17: 0.53</td>
<td>BRI rating high risk: 0.43</td>
<td>ORT score ≥ 4: 0.54 (also reported as 0.57)</td>
<td>SOAPP-R score &gt; 17: 0.62</td>
<td>BRI high risk: 1.28</td>
</tr>
<tr>
<td>Jones, 2014</td>
<td>BRI high risk (rating medium to very high): 10</td>
<td>ORT score ≥ 4: 16</td>
<td>SOAPP-R score &gt; 17: 30</td>
<td>SOAPP-R score &gt; 17: 92</td>
<td>BRI high risk: 0.83 (95% CI, 0.52 to 0.98)</td>
<td>ORT score ≥ 4: 0.52 to 0.94</td>
<td>SOAPP-R score &gt; 17: 0.75 (95% CI, 0.43 to 0.95)</td>
<td>SOAPP-R score &gt; 17: 0.25 (95% CI, 0.055 to 0.57)</td>
<td>BRI high risk: 0.88 (95% CI, 0.81 to 0.94)</td>
<td>ORT score ≥ 4: 0.86 (95% CI, 0.78 to 0.92)</td>
</tr>
</tbody>
</table>

Table H-39 Key Question 4: Prospective Studies on Use of Screening Instruments to Predict the Risk of Aberrant Drug-related Behaviors - study results
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>True Positives (n)</th>
<th>False Positives (n)</th>
<th>True Negatives (n)</th>
<th>False Negatives (n)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
<th>AUROC</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones, 2015</td>
<td>BRI high risk</td>
<td>59</td>
<td>BRI high risk</td>
<td>93</td>
<td>0.79 (95% CI, 0.68 to 0.87)</td>
<td>0.51 (95% CI, 0.44 to 0.59)</td>
<td>1.61 (95% CI, 1.33 to 1.94)</td>
<td>0.32 (95% CI, 0.22 to 0.44)</td>
<td>0.83 (95% CI, 0.70 to 0.83)</td>
<td>0.42 (95% CI, 0.26 to 0.66)</td>
</tr>
<tr>
<td>Moore, 2009</td>
<td>SOAPP: 35</td>
<td>Not calculable</td>
<td>Not calculable</td>
<td>Not calculable</td>
<td>0.73</td>
<td>0.45</td>
<td>Clinical interview: 11</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Webster, 2005</td>
<td>ORT score 1 to 3</td>
<td>1</td>
<td>ORT score 1 to 3</td>
<td>1</td>
<td>0.08 (95% CI, 0.01 to 0.62)</td>
<td>0.16 (95% CI, 0.10 to 0.24)</td>
<td>0.17 (95% CI, 1.07 to 1.27)</td>
<td>0.57 (95% CI, 0.44 to 0.74)</td>
<td>0.17 (95% CI, 0.70 to 0.83)</td>
<td>0.08 (95% CI, 0.01 to 0.65)</td>
</tr>
<tr>
<td></td>
<td>(low risk): 1</td>
<td>(low risk): 17</td>
<td>(low risk): 92</td>
<td>(low risk): 92</td>
<td>0.09 (95% CI, 0.92 to 0.999)</td>
<td>1.17 (95% CI, 1.07 to 1.27)</td>
<td>0.08 (95% CI, 0.01 to 0.62)</td>
<td>0.57 (95% CI, 0.44 to 0.74)</td>
<td>0.17 (95% CI, 0.70 to 0.83)</td>
<td>0.08 (95% CI, 0.01 to 0.65)</td>
</tr>
<tr>
<td></td>
<td>ORT score 4 to 7</td>
<td>(moderate risk): 35</td>
<td>ORT score 4 to 7</td>
<td>(moderate risk): 21</td>
<td>0.99 (95% CI, 0.92 to 0.999)</td>
<td>1.17 (95% CI, 1.07 to 1.27)</td>
<td>0.08 (95% CI, 0.01 to 0.62)</td>
<td>0.57 (95% CI, 0.44 to 0.74)</td>
<td>0.17 (95% CI, 0.70 to 0.83)</td>
<td>0.08 (95% CI, 0.01 to 0.65)</td>
</tr>
<tr>
<td></td>
<td>(high risk): 40</td>
<td>(high risk): 40</td>
<td>(high risk): 40</td>
<td>(high risk): 40</td>
<td>0.99 (95% CI, 0.92 to 0.999)</td>
<td>1.17 (95% CI, 1.07 to 1.27)</td>
<td>0.08 (95% CI, 0.01 to 0.62)</td>
<td>0.57 (95% CI, 0.44 to 0.74)</td>
<td>0.17 (95% CI, 0.70 to 0.83)</td>
<td>0.08 (95% CI, 0.01 to 0.65)</td>
</tr>
</tbody>
</table>

Abbreviations: AUROC=area under the receiver operator curve; BRI=Brief Risk Interview; BRQ=Brief Risk Questionnaire; CI=confidence interval; DIRE=Diagnosis, Intractability, Risk, Efficacy score; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SD=standard deviation; SOAPP=Screener and Opioid Assessment for Patients with Pain; SOAPP-R=Screener and Opioid Assessment for Patients with Pain-Revised.
See Appendix F. Included Studies for full citations
### Table H-40. Key Question 4: Study of co-prescription of naloxone in persons prescribed opioids for chronic pain

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Type of Study, Setting</th>
<th>Eligibility criteria</th>
<th>Comparison Groups</th>
<th>Sample Characteristics</th>
<th>Method For Assessing Outcomes and Confounders</th>
<th>Enrolled Analyzed Loss to Followup</th>
<th>Adjusted Variables For Statistical Analysis</th>
<th>Main Results</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffin, 2016</td>
<td>Retrospective cohort 6 primary care clinics in San Francisco, USA</td>
<td>Pain condition: Not specified Age: ≥18 years Pain severity: Not specified Psychiatric disorder: Not specified Substance use: Not specified Prior opioid use: Yes</td>
<td>A. Co-prescribed naloxone B. Not co-prescribed naloxone</td>
<td>A vs. B Mean (SD) age, years: 55.7 (10.7) vs. 57.3 (10.8) Female: 42% vs. 41% White: 35.3% vs. 27.5% Black: 44.5% vs. 50.7% Hispanic: 11.9% vs. 14.3% Other race: 8.3% vs. 7.4% Median opioid dose: 53 mg MED/day (range: 2 to 4200)</td>
<td>Multivariable Poisson regression model was used for the monthly number of opioid-related ED visits, using an offset to account for days of exposure in each month. The model used GEE with exchangeable working correlation and robust SEs to account for clustering by patient, as well as over dispersion.</td>
<td>Enrolled: 1985 (759 vs. 1226) Analyzed: 1985 (759 vs. 1226) Loss to followup: Not reported</td>
<td>The model adjusted for age, race/ethnicity, sex, MED at baseline, history of any opioid-related ED visit between January 1, 2012 and December 31, 2012, and clinic.</td>
<td>A vs. B, RR (95% CI) All-cause mortality: 2.5% (19/759) vs. 3.3% (40/1226), RR 0.77 (0.45 to 1.31) Opioid poisoning deaths: 0.3% (2/759) vs. 0.2% (3/1226), RR 1.08 (0.18 to 6.4) Opioid related ED visits per month, IRR (95% CI): 0.94 (0.89 to 0.998), p=0.044; 6% reduction Opioid related ED visits per month 6 months after given prescription, IRR (95% CI): 0.53 (0.34 to 0.83), p=0.005; 47% reduction Opioid related ED visits per month 1 year after given prescription, IRR (95% CI): 0.37 (0.22 to 0.64), p&lt;0.001; 63% reduction</td>
<td>NIH</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; ED=emergency department; GEE=generalized estimating equation; MED=morphine equivalent dose; NIH=National Institutes of Health; RR=risk ratio; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations

H-83
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design Duration</th>
<th>Setting Country</th>
<th>Eligibility criteria</th>
<th>Interventions</th>
<th>Sample Characteristics</th>
<th>Screened Eligible Randomized Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondell, 2010</td>
<td>Open-label, RCT 6 months</td>
<td>Setting not described, USA</td>
<td>Men and women aged ≥18 years with well documented chronic non-cancer pain and self-identified addiction to prescription opioids referred by physicians associated with study site program</td>
<td>Potential participants asked to stop taking all opioid medications evening prior to hospitalization for stabilization; following admission, patients given 4 mg buprenorphine sublingually after opiate withdrawal signs and increased by 2 mg every 2 hours until withdrawal improved. Goal was to reduce pain in 24 to 48 hours on stable dose of buprenorphine/naloxone 2 mg/0.5 mg 3 to 4 times daily. A. Steady dose buprenorphine at time of hospital discharge to be continued for entire 6 month followup; patients during first 4 weeks were permitted to increase dose to 16 mg/day; participants could opt out and switch to tapering protocol B. Tapering doses of buprenorphine over 4 months, then all opioids to be discontinued for 2 months-permitted to increase starting dose up to 16 mg; also permitted to opt out of tapering protocol and initiate steady dose schedule during the 4 month of followup</td>
<td>Mean (SD) age, year: 44 (6.4) vs. 46 (14.6) Female: 50% White: 92% History of alcohol use only: 33% History of alcohol and drug abuse: 33% Prior SUD treatment: 42%</td>
<td>Screened: 12 Enrolled: 12 1 drop out of study 1 relapsed to illicit drug use and lost to followup</td>
</tr>
<tr>
<td>Fiellin, 2014</td>
<td>Open-label RCT 14 weeks</td>
<td>Primary care center of Yale-New Haven Hospital, USA</td>
<td>Pain condition: Mixed Age: Not specified Pain severity: Not specified Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: Yes, dose not specified</td>
<td>A. Buprenorphine taper (target dose of 16 mg/day) B. Buprenorphine maintenance</td>
<td>A vs. B Mean (95% CI) age, years: 30.3 (28.0 to 32.6) vs. 30.5 (27.9 to 33.1) Female: 40% vs. 50% White: 98% vs. 93% Hispanic: 7% vs. 7% Mean (95% CI) duration of opioid dependence, years: 4.5 (3.3 to 5.6) vs. 4.9 (3.7 to 6.0)</td>
<td>Screened: NR Eligible: NR Randomized: 113 (57 vs. 56) Analyzed: 113 (57 vs. 56)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design</td>
<td>Duration</td>
<td>Setting Country</td>
<td>Eligibility criteria</td>
<td>Interventions</td>
<td>Sample Characteristics</td>
</tr>
<tr>
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<td>------------------------</td>
</tr>
<tr>
<td>Neumann, 2013</td>
<td>RCT</td>
<td>6 months</td>
<td>Unclear, USA</td>
<td>Pain condition: Pain related to the spine or a large joint Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded Substance use: Not specified Prior opioid use: Yes, but dose not specified</td>
<td>A. Buprenorphine (4 to 16 mg/day) + naloxone (1 to 4 mg/day) sublingually. B. Methadone oral tablets (10 to 60 mg/day), 1 to 4 doses daily</td>
<td>Mean (SD) age, years: 39.0 (10.9) vs. 37.7 (8.6) Female: 34.6% vs. 57.1% White: 76.9% vs. 92.9% Mean (SD) pain score: 5.9 (2.1) vs. 6.9 (1.4) Mean (SD) functioning score: 4.4 (2.0) vs. 5.6 (1.7) Mean (SD) age of onset of opioid use, years: 31.2 (11.2) vs. 28.0 (6.5) Positive urine for opiates: 38.5% vs. 35.7%</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; NR=not reported; SD=standard deviation; SUD=substance use disorder; USA=United States of America; vs.=versus. See Appendix F. Included Studies for full citations
### Table H-42. Key Question 4: Studies of Treatment Strategies for Managing Patients with Opioid Use Disorder Related to Prescription Opioids - study results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Adverse Events and Discontinuation Due To Adverse Events</th>
<th>Funding Source</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blondell, 2010</td>
<td>Mean stable dose of buprenorphine: 7.5 mg/day at hospital discharge; 9.8 mg/day at 4 weeks Study terminated early because none of the 6 participants in tapering dose arm could complete the 6-month protocol -5 switched to stable dose arm (2 in month 1; 1 in month 2; 1 in month 3; 1 in month 4) -1 was admitted to inpatient unit after relapse after 2nd month (terminated due to ethical reasons) In the stable dose arm, 5 completed 6-month protocol and 1 withdrew due to cost of medication. (0/6 vs. 5/6 completed, p=0.015) At 6 month followup: 10 participants completed 5 and 5; 8 receiving opioid replacement therapy, 6 reported improved pain control and physical functioning.</td>
<td>1 discontinued due to relapse; no other reported events</td>
<td>National Institute on Alcohol Abuse and Alcoholism, Donald W. Reynolds Foundation</td>
<td>Poor</td>
</tr>
<tr>
<td>Fiellin, 2014</td>
<td>A vs. B Urine samples negative for opioids: 35.2% (95% CI, 26.2% to 44.2%) vs. 53.2% (95% CI, 44.3% to 62.05%) Mean (95% CI) days per week of illicit opioid use during last 7 weeks of trial once they were no longer receiving buprenorphine: 1.27 (0.60 to 1.94) vs. 0.47 (0.19 to 0.74) Mean (95% CI) maximum consecutive weeks of opioid abstinence: 2.70 (1.72 to 3.75) vs. 5.20 (4.16 to 6.20) Relapse with protective transfer: 28% vs. 5%, p=0.001</td>
<td>A vs. B Discontinued study: 89% vs. 34%, p&lt;0.001</td>
<td>National Institute on Drug Abuse</td>
<td>Fair</td>
</tr>
<tr>
<td>Neumann, 2013</td>
<td>A vs. B, change from baseline at 24 weeks Pain (0 to 10), mean (SD): 87.4% (33.4) vs. 88.6% (24.5) Function (0 to 10), mean (SD): 121.9% (63.9) vs. 113.8% (62.5)</td>
<td>A vs. B Any self-reported side effect: 61.5% (8/13) vs. 69.2% (9/13); OR, 1.125 (95% CI, 0.209 to 6.046) Others of interest: NR</td>
<td>Government</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; NR=not reported; OR=odds ratio; SD=standard deviation; vs.=versus.  
See Appendix F. Included Studies for full citations
# Appendix I. Strength of Evidence

## Table I-1. Strength of evidence and key findings*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcomes</th>
<th>Number of studies</th>
<th>Number of subjects</th>
<th>Directness</th>
<th>Precision</th>
<th>Study limitations</th>
<th>Consistency</th>
<th>Findings† (95% CI)</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid vs. placebo or no opioid therapy</td>
<td>Pain (short-term)</td>
<td>70 RCTs (continuous); 43 RCTs (dichotomous)</td>
<td>19,486 (continuous); 12,351 (dichotomous)</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>MD: -0.80 (-0.94 to -0.67); RR: 1.35 (1.24 to 1.49)</td>
<td>High†</td>
</tr>
<tr>
<td>Function (short-term)</td>
<td>43 RCTs</td>
<td>12,297</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>SMD: -0.22 (-0.28 to -0.16)</td>
<td>High‡</td>
<td></td>
</tr>
<tr>
<td>SF-36 physical (short-term)</td>
<td>22 RCTs</td>
<td>7875</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>MD: 1.65 (1.09 to 2.18)</td>
<td>High‡</td>
<td></td>
</tr>
<tr>
<td>SF-36 mental (short-term)</td>
<td>20 RCTs</td>
<td>7456</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>MD: -0.52 (-1.45 to 0.41)</td>
<td>High‡</td>
<td></td>
</tr>
<tr>
<td>Sleep quality (short-term)</td>
<td>24 RCTs</td>
<td>6590</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>SMD: -0.25 (95% CI: -0.33 to -0.19)</td>
<td>Moderate‡</td>
<td></td>
</tr>
<tr>
<td>Depression (short-term)</td>
<td>5 RCTs</td>
<td>1079</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
<td>Consistent</td>
<td>SMD: 0.00 (-0.22 to 0.18)</td>
<td>Moderate‡</td>
<td></td>
</tr>
<tr>
<td>Anxiety (short-term)</td>
<td>2 RCTs</td>
<td>229</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>MD: 0.60 (-3.58 to 1.82)</td>
<td>Low‡</td>
<td></td>
</tr>
<tr>
<td>Pain and function (long-term)</td>
<td>1 cohort study</td>
<td>529</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No differences at 2 years</td>
<td>Low‡</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>80 RCTs</td>
<td>19,864</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 2.26 (1.87 to 2.75)</td>
<td>High†</td>
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</tr>
<tr>
<td>Serious AEs</td>
<td>37 RCTs</td>
<td>13,030</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 1.21 (0.87 to 1.71)</td>
<td>Moderate‡</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>80 RCTs</td>
<td>19,718</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 2.46 (2.17 to 2.80)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>49 RCTs</td>
<td>17,388</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 3.57 (2.98 to 4.34)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>58 RCTs</td>
<td>19,351</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 3.38 (2.96 to 3.92)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>53 RCTs</td>
<td>18,396</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 2.66 (2.37 to 2.99)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>48 RCTs</td>
<td>17,405</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 1.06 (0.95 to 1.17)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>52 RCTs</td>
<td>17,458</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 2.66 (2.37 to 2.99)</td>
<td>High†</td>
<td></td>
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<tr>
<td>Pruritus</td>
<td>30 RCTs</td>
<td>11,454</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR: 3.51 (2.47 to 5.16)</td>
<td>High†</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<td>------------</td>
<td>-----------</td>
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<td>-------------</td>
<td>--------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Opioid vs. placebo or no opioid therapy, continued</strong></td>
<td>Opioid abuse, dependence, or addiction</td>
<td>2 cohort studies</td>
<td>666,780</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioids associated with increased risk</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Overdose</td>
<td>2 cohort studies</td>
<td>108,080</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioids associated with increased risk</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>1 cohort study</td>
<td>22,912</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Opioids associated with increased risk</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Fracture</td>
<td>5 observational</td>
<td>38,750</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioids associated with increased risk</td>
<td>Low</td>
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<tr>
<td></td>
<td>Cardiovascular events</td>
<td>3 cohort studies</td>
<td>505,626</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioids associated with increased risk</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Endocrinological harms</td>
<td>1 cross-sectional</td>
<td>11,327</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Unable to determine</td>
<td>Insufficient</td>
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<tr>
<td><strong>Opioids vs. nonopioids</strong></td>
<td>Pain (short-term)</td>
<td>12 RCTs (continuous); 11 RCTs (dichotomous)</td>
<td>1879 (continuous); 2646 (dichotomous)</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>MD -0.18 (-0.52 to 0.14); RR 1.06 (0.88 to 1.32)</td>
<td>Moderate†</td>
</tr>
<tr>
<td></td>
<td>Function (short-term)</td>
<td>9 RCTs</td>
<td>1694</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD 0.05 (-0.10 to 0.17)</td>
<td>High†</td>
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<tr>
<td></td>
<td>SF-36 physical (short-term)</td>
<td>8 RCTs</td>
<td>1423</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>MD -1.80 (-5.45 to -4.02)</td>
<td>Moderate†</td>
</tr>
<tr>
<td></td>
<td>SF-36 mental (short-term)</td>
<td>8 RCTs</td>
<td>1427</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>MD -0.63 (-4.27 to 0.91)</td>
<td>Moderate†</td>
</tr>
<tr>
<td></td>
<td>Sleep quality (short-term)</td>
<td>8 RCTs</td>
<td>1454</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD 0.01 (-0.14 to 0.12)</td>
<td>Moderate†</td>
</tr>
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<td>Depression (short-term)</td>
<td>7 RCTs</td>
<td>748</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD 0.05 (-0.09 to 0.22)</td>
<td>Moderate†</td>
</tr>
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<td>Anxiety (short-term)</td>
<td>3 RCTs</td>
<td>414</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD 0.00 (-0.62 to 0.36)</td>
<td>Low‡</td>
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<tr>
<td></td>
<td>Discontinuation due to AEs</td>
<td>10 RCTs</td>
<td>3289</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 2.58 (1.76 to 3.54)</td>
<td>High†</td>
</tr>
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<td>Serious AEs</td>
<td>4 RCTs</td>
<td>1949</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 0.63 (0.08 to 4.87)</td>
<td>Moderate†</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>10 RCTs</td>
<td>3029</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 2.67 (1.97 to 3.94)</td>
<td>High†</td>
</tr>
<tr>
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<td>Vomiting</td>
<td>5 RCTs</td>
<td>2536</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 4.50 (2.75 to 7.22)</td>
<td>High†</td>
</tr>
<tr>
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<td>Constipation</td>
<td>10 RCTs</td>
<td>3029</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 3.63 (2.47 to 5.15)</td>
<td>High†</td>
</tr>
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<td>Dizziness</td>
<td>10 RCTs</td>
<td>3029</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 1.87 (1.22 to 2.51)</td>
<td>High†</td>
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<tr>
<td>Intervention</td>
<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
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</tr>
<tr>
<td>Opioids vs. nonopioids, continued</td>
<td>Headache</td>
<td>7 RCTs</td>
<td>2683</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 1.36 (1.09 to 1.74)</td>
<td>High†</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>10 RCTs</td>
<td>3029</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 2.68 (2.03 to 3.58)</td>
<td>High†</td>
</tr>
<tr>
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<td>Pruritus</td>
<td>5 RCTs</td>
<td>2577</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>RR 4.22 (2.45 to 6.20)</td>
<td>High†</td>
</tr>
<tr>
<td></td>
<td>Opioid abuse, dependence, or addiction</td>
<td>No studies</td>
<td>--</td>
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<tr>
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<td>Overdose</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>No studies</td>
<td>--</td>
<td>--</td>
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<td>--</td>
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</tr>
<tr>
<td></td>
<td>Fracture</td>
<td>No studies</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>Cardiovascular events</td>
<td>No Studies</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>Endocrinological harms</td>
<td>No studies</td>
<td>--</td>
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</tr>
<tr>
<td>Opioid + nonopioid vs. nonopioid</td>
<td>Pain (short-term)</td>
<td>5 RCTs (continuous); 5 RCTs (dichotomous)</td>
<td>325 (continuous); 462 (dichotomous)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>MD 0.00 (-0.67 to 0.68); RR 1.15 (0.83 to 1.54)</td>
<td>Low†</td>
</tr>
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<td>Function (short-term)</td>
<td>3 RCTs</td>
<td>246</td>
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<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.05 (-0.31 to 0.21)</td>
<td>Low†</td>
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<td>SF-36 physical (short-term)</td>
<td>4 RCTs</td>
<td>297</td>
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<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD 0.58 (-4.19 to 4.37)</td>
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<td>SF-36 mental (short-term)</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>SMD -2.92 (-6.32 to 0.57)</td>
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<td>Sleep quality (short-term)</td>
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<td>143</td>
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<td>Consistent</td>
<td>SMD 0.05 (-0.52 to 0.72)</td>
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<td>Consistent</td>
<td>SMD -0.01 (-0.31 to 0.26)</td>
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<td>Anxiety (short-term)</td>
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<td>Discontinuation due to AEs</td>
<td>5 RCTs</td>
<td>404</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>RR 3.03 (1.37 to 5.15)</td>
<td>Moderate†</td>
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<td>1 RCT</td>
<td>62</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unable to assess</td>
<td>RR 0.38 (0.02 to 8.83)</td>
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<td>Nausea</td>
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<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 2.18 (1.16 to 4.49)</td>
<td>Moderate†</td>
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<td>Vomiting</td>
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<td>81</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.68 (0.43 to 6.56)</td>
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<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings(^\d) (95% CI)</td>
<td>SOE</td>
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<td><strong>Opioid + nonopioid vs. nonopioid, continued</strong></td>
<td>Constipation</td>
<td>5 RCTs</td>
<td>330</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 3.23 (2.10 to 7.57)</td>
<td>Moderate(^\d)</td>
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<td>Dizziness</td>
<td>5 RCTs</td>
<td>330</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.38 (0.56 to 2.11)</td>
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<td>137</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.18 (0.42 to 3.00)</td>
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<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 2.44 (1.32 to 4.52)</td>
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<td>Pruritus</td>
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<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 3.49 (0.32 to 37.88)</td>
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<td>Overdose</td>
<td>No studies</td>
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<td>All-cause mortality</td>
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<tr>
<td></td>
<td>Fracture</td>
<td>No studies</td>
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<td>Cardiovascular events</td>
<td>No studies</td>
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<td></td>
<td>Endocrinological harms</td>
<td>No studies</td>
<td>--</td>
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<tr>
<td><strong>Opioid + nonopioid vs. opioid alone</strong></td>
<td>Pain (short-term)</td>
<td>5 RCTs (continuous); 5 RCTs (dichotomous)</td>
<td>623 (continuous); 831 (dichotomous)</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>MD -0.40 (-0.72 to -0.07); RR 1.19 (0.97 to 1.68)</td>
<td>Low(^\d)</td>
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<td>Function</td>
<td>4 RCTs</td>
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<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.25 (-0.49 to 0.09)</td>
<td>Low(^\d)</td>
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<td>SF-36 physical (short-term)</td>
<td>4 RCTs</td>
<td>553</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.19 (-2.48 to 4.08)</td>
<td>Low(^\d)</td>
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<td>SF-36 mental (short-term)</td>
<td>6 RCTs</td>
<td>1381</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.63 (-4.27 to 3.91)</td>
<td>Low(^\d)</td>
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<td>Direct</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.10 (-0.38 to 0.14)</td>
<td>Low(^\d)</td>
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<td>Depression (short-term)</td>
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<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.18 (-0.37 to -0.01)</td>
<td>Low(^\d)</td>
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<td>Anxiety (short-term)</td>
<td>1 RCT</td>
<td>278</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>SMD -0.04 (-0.28 to 0.19)</td>
<td>Insufficient(^\d)</td>
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<td>Discontinuation due to AEs</td>
<td>5 RCTs</td>
<td>782</td>
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<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.79 (0.50 to 1.27)</td>
<td>Low(^\d)</td>
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<td>Serious AEs</td>
<td>1 RCT</td>
<td>313</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.58 (0.14 to 2.39)</td>
<td>Insufficient(^\d)</td>
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<td>Intervention</td>
<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
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<tr>
<td>Opioid + non-opioid vs. opioid alone, continued</td>
<td>Nausea</td>
<td>5 RCTs</td>
<td>585</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.98 (0.57 to 1.84)</td>
<td>Low†</td>
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<td>Vomiting</td>
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<td>339</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.68 (0.34 to 8.19)</td>
<td>Low†</td>
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<tr>
<td></td>
<td>Constipation</td>
<td>5 RCTs</td>
<td>860</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.91 (0.67 to 1.13)</td>
<td>Low†</td>
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<tr>
<td></td>
<td>Dizziness</td>
<td>5 RCTs</td>
<td>772</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.22 (0.23 to 1.99)</td>
<td>Low†</td>
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<td>Headache</td>
<td>3 RCTs</td>
<td>457</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 1.12 (0.46 to 2.25)</td>
<td>Low†</td>
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<td>Somnolence</td>
<td>6 RCTs</td>
<td>860</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.74 (0.40 to 1.30)</td>
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<td>Pruritus</td>
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<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>RR 0.24 (0.03 to 1.91)</td>
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<td>Opioid abuse, dependence, or addiction</td>
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<td>Overdose</td>
<td>No studies</td>
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<td>Fracture</td>
<td>No studies</td>
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<td>Endocrinological harms</td>
<td>No studies</td>
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<td>Opioid + cannabis vs. opioid</td>
<td>Pain, function, opioid discontinuation, opioid dose</td>
<td>1 observational study</td>
<td>1514</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unable to assess</td>
<td>No association</td>
<td>Low†</td>
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<td>Opioid + benzodiazepine vs. opioid</td>
<td>Overdose</td>
<td>3 observational studies</td>
<td>140,002</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioid + benzodiazepine associated with increased risk</td>
<td>Low†</td>
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<td>Opioid + gabapentinooid vs. opioid</td>
<td>Overdose</td>
<td>3 observational studies</td>
<td>799,013</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Opioid + gabapentinooid associated with increased risk</td>
<td>Low†</td>
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<td>Methods for initiating and titrating opioids</td>
<td>Pain</td>
<td>2 RCTs</td>
<td>81</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>Unable to assess</td>
<td>Insufficient</td>
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<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
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<tr>
<td>Methods for initiating and titrating opioids, continued</td>
<td>Opioid use disorder or related outcomes</td>
<td>No studies</td>
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<td><strong>Short-acting vs. long-acting opioids</strong></td>
<td>Pain, function</td>
<td>2 RCTs</td>
<td>184</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Consistent</td>
<td>No differences</td>
<td>Low†</td>
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<td></td>
<td>Overdose</td>
<td>1 cohort study</td>
<td>840,606</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Long-acting associated with increased risk</td>
<td>Low†</td>
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<td><strong>Long-acting opioid vs. a different long-acting opioid</strong></td>
<td>Pain, function, and other effectiveness outcomes</td>
<td>16 RCTs</td>
<td>7356</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>No patterns showing differential effectiveness, with some differences in opioid dosing between arms</td>
<td>Moderate†</td>
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<td></td>
<td>Overdose</td>
<td>4 cohort studies</td>
<td>193,166</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Methadone associated with increased risk vs. morphine in 2 studies of Medicaid patients and decreased risk in 1 study of VA patients</td>
<td>Low†</td>
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<tr>
<td><strong>Short + long-acting opioid vs. long-acting opioid alone</strong></td>
<td>All</td>
<td>No studies</td>
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<td><strong>Scheduled, continuous vs. as-needed dosing</strong></td>
<td>All</td>
<td>No studies</td>
<td>--</td>
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<tr>
<td><strong>Opioid dose escalation vs. dose maintenance</strong></td>
<td>Pain, function</td>
<td>1 RCT</td>
<td>140</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No differences; doses were similar in the two arms</td>
<td>Low</td>
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<td><strong>Opioid withdrawal due to misuse</strong></td>
<td>1 RCT</td>
<td>140</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No difference</td>
<td>Low</td>
<td></td>
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<tr>
<td><strong>Opioid rotation vs. maintenance of current opioid therapy</strong></td>
<td>All</td>
<td>No studies</td>
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<td>Intervention</td>
<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
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<tr>
<td>Strategies for treating acute exacerbations of chronic pain</td>
<td>Pain (immediate)</td>
<td>4 RCTs</td>
<td>476</td>
<td>Direct</td>
<td>Precise</td>
<td>Low</td>
<td>Consistent</td>
<td>Buccal fentanyl more effective than placebo or oral opioid for immediate pain relief</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Longer-term outcomes, addiction, abuse</td>
<td>No studies</td>
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<tr>
<td>Tapering off opioids vs. continuation of opioids</td>
<td>Pain, function</td>
<td>1 RCT</td>
<td>34</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No differences</td>
<td>Low†</td>
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<tr>
<td></td>
<td>Opioid dose</td>
<td>1 RCT</td>
<td>34</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Taper associated with lower dose</td>
<td>Low†</td>
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<tr>
<td>Tapering protocols and strategies</td>
<td>Pain, tapering completion, opioid withdrawal</td>
<td>1 RCT</td>
<td>21</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Varenicline associated with no differences versus placebo as an adjunct to tapering</td>
<td>Low†</td>
</tr>
<tr>
<td></td>
<td>Opioid-related emergency department visit</td>
<td>1 cohort study</td>
<td>494</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Each additional week to discontinuation associated with 7% reduction in risk</td>
<td>Low</td>
</tr>
<tr>
<td>Opioid Risk Tool</td>
<td>Diagnostic accuracy</td>
<td>6 studies</td>
<td>1025</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Sensitivity: 0.20 to 0.99 Specificity: 0.16 to 0.88</td>
<td>Low†</td>
</tr>
<tr>
<td>SOAPP Version 1</td>
<td>Diagnostic accuracy</td>
<td>2 studies</td>
<td>203</td>
<td>Direct</td>
<td>Imprecise</td>
<td>High</td>
<td>Consistent</td>
<td>Sensitivity: 0.68 and 0.73 Specificity: 0.38</td>
<td>Low</td>
</tr>
<tr>
<td>SOAPP-R</td>
<td>Diagnostic accuracy</td>
<td>4 studies</td>
<td>840</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Inconsistent</td>
<td>Sensitivity: 0.25 to 0.53 Specificity: 0.62 to 0.77</td>
<td>Low†</td>
</tr>
<tr>
<td>Brief Risk Interview</td>
<td>Diagnostic accuracy</td>
<td>3 studies</td>
<td>577</td>
<td>Direct</td>
<td>Precise</td>
<td>High</td>
<td>Inconsistent</td>
<td>Sensitivity 0.73 to 0.83 Specificity: 0.43 to 0.88</td>
<td>Low†</td>
</tr>
<tr>
<td>Intervention</td>
<td>Outcomes</td>
<td>Number of studies</td>
<td>Number of subjects</td>
<td>Directness</td>
<td>Precision</td>
<td>Study limitations</td>
<td>Consistency</td>
<td>Findings† (95% CI)</td>
<td>SOE</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>Naloxone co-prescription</td>
<td>Emergency department visits</td>
<td>1 nonrandomized study</td>
<td>1985</td>
<td>Direct</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Naloxone associated with decreased risk of emergency department visits versus no naloxone</td>
<td>Low†</td>
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<tr>
<td>All-cause mortality, opioid poisoning deaths</td>
<td>1 nonrandomized study</td>
<td>1985</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No difference</td>
<td>Low†</td>
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</tr>
<tr>
<td>Prescription opioid use disorder: Taper vs. maintenance</td>
<td>Drug use</td>
<td>1 RCT</td>
<td>113</td>
<td>Indirect</td>
<td>Precise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Buprenorphine taper inferior to maintenance</td>
<td>Low†</td>
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<tr>
<td>Prescription opioid use disorder: Buprenorphine vs. methadone</td>
<td>Drug use, pain function</td>
<td>1 RCT</td>
<td>54</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Moderate</td>
<td>Unknown</td>
<td>No differences</td>
<td>Low†</td>
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</tbody>
</table>

Abbreviations: AE=adverse events; CI=confidence interval; MD=mean difference; RCT=randomized controlled trial; RR=risk ratio; SMD=standard mean difference; SOE=strength of evidence; SOAPP=Screening and Opioid Assessment for Patients with Pain; SOAPP-R=Screening and Opioid Assessment for Patients with Pain-Revised Version; VA=Veterans Affairs Department; vs.=versus.

* Reporting bias was undetected for all key questions/outcomes
† Mean differences for pain are reported on a 0 to 10 scale and for SF-36 measures are reported on a 0 to 100 scale
‡ Not addressed in the prior AHRQ report
§ Graded down for potential reporting bias
¶ The SOE was insufficient in the prior AHRQ report
ǁ The SOE was low in the prior AHRQ report