Opioids for chronic noncancer pain: Key questions for systematic evidence review

Risk-benefit assessment
1. In patients being considered for opioids for chronic non-cancer pain, how accurate are patient features or characteristics for predicting:
   a. Benefits of chronic opioid therapy?
   b. Opioid-related harms?
   c. Aberrant drug-related behaviors?
2. In patients being considered for opioids for chronic non-cancer pain, how accurate are formal screening instruments for predicting benefits of opioid therapy, harms, or aberrant drug-related behaviors?
3. In patients being considered for opioids for chronic non-cancer pain, how effective is risk assessment for:
   a. Improving clinical outcomes?
   b. Reducing risk of aberrant drug behaviors?

Benefits and harms
4. What are the benefits (including long-term benefits) of opioids for chronic non-cancer pain?
5. What are the harms (including long-term harms) of opioids for chronic non-cancer pain? In patients at higher risk for abuse or addiction?
6. What are the benefits and harms of opioids for non-cancer pain in patients with a history of substance abuse or addiction that are undergoing treatment for addiction?
7. What are the comparative benefits and harms of different opioids and different formulations of opioids for chronic non-cancer pain?
8. Do the comparative benefits and harms of opioids vary in subpopulations defined by demographics (e.g., age, gender, race), specific underlying pain conditions, or co-morbidities (e.g., liver disease, renal disease, respiratory disease, heart disease, HIV, drug misuse, cancer survivors)?
9. How effective are different strategies for minimizing or treating opioid-related adverse events?
10. How does initial or chronic use of opioids impact driving or work safety?

Opioid dosing strategies
11. What are the benefits and harms of different methods for initiating and titrating opioids for chronic non-cancer pain?
12. What are the benefits and harms of round-the-clock versus as needed dosing of opioids, or round-the-clock with as needed dosing versus as needed dosing alone for chronic non-cancer pain?
13. What are the benefits and harms of regular intramuscular, subcutaneous, intranasal, buccal, or rectal versus oral or transdermal administration of opioids for chronic non-cancer pain?
14. What are the comparative benefits of different strategies for treating acute exacerbations of pain or a new acute pain problem in patients on chronic opioids for chronic non-cancer pain?
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15. What are the benefits and harms of opioid rotation versus continued treatment or dose escalation with the same opioid in patients with chronic non-cancer pain?

16. What are the benefits and harms of different methods for switching patients on opioids for chronic non-cancer pain from one opioid to another?

17. How accurate are patient characteristics or features for predicting lack of response to high doses of opioids for chronic non-cancer pain?

18. How do dose-related responses for opioids change at different dose ranges or with long-term use?

19. What are the benefits and harms of high (>200 mg/day of morphine or equivalent) versus lower doses of opioids for chronic non-cancer pain?

20. Are high doses of opioids associated with different or unique harms compared to lower doses?

Co-interventions and adjunctive interventions

21. How effective are patient education methods or clinician advice for improving outcomes associated with chronic opioid therapy?

22. How effective is co-prescription with other pain-attenuating medications or combining opioids for improving pain control or decreasing adverse events associated with opioid analgesics?

23. What is the effect of concomitant use of drugs with CNS effects on adverse events associated with opioids for chronic non-cancer pain?

24. What are the benefits associated with behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration/work hardening in addition to or instead of opioids for chronic non-cancer pain?

Methods for monitoring opioid use and detecting aberrant drug-related behaviors

25. How effective are opioid agreements/contracts for improving clinical benefits and reducing harms, including abuse, addiction, or other aberrant drug-related behaviors associated with opioids for chronic non-cancer pain?

26. In patients receiving opioids for chronic non-cancer pain, how accurate are formal screening instruments for identifying aberrant drug-related behaviors?

27. In patients receiving opioids for chronic non-cancer pain, what is the diagnostic accuracy of urine drug screening and different urine drug screening methods for:
   a. Detecting illicit drug use?
   b. Identifying the presence or absence of prescribed and non-prescribed opioids and estimating doses of opioids?

28. In patients receiving opioids for chronic non-cancer pain, how effective is urine drug screening and different urine drug screen methods for reducing abuse, addiction, and other aberrant drug-related behaviors, or increasing adherence to taking opioids as prescribed?
29. In patients receiving opioids for chronic non-cancer pain, how effective are other methods (pill counts, limited prescriptions, monitoring blood levels) for detecting or reducing abuse, addiction, other aberrant drug-related behaviors, or whether patients are taking opioids as prescribed?

30. Is re-evaluation of patients on chronic opioid therapy at different intervals associated with different outcomes?

31. What are the benefits and harms associated with different methods for evaluating outcomes in patients receiving opioids for chronic non-cancer pain?

32. In patients receiving opioids for chronic non-cancer pain, what is the accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors?

33. In patients receiving opioids for chronic non-cancer pain, what is the effect of diagnosing drug-related behaviors due to inadequate symptom relief on clinical outcomes?

**Discontinuing opioids**

34. What patient features or characteristics predict improved outcomes with discontinuation of long-term opioids versus continued treatment?

35. What are the benefits and harms of different methods for discontinuing opioids?

**Pregnancy**

36. What are the benefits and harms of continuing opioids versus switching to alternative analgesics in women with chronic non-cancer pain who become pregnant or are planning to become pregnant?

**Opioid prescribing policies**

37. What are the benefits and harms of opioid prescribing policies on clinical outcomes?
Definitions for estimating magnitude of effects

<table>
<thead>
<tr>
<th>Size of effect</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Small/ slight</td>
<td>5-10 improvement on a 100 point scale SMD 0.2 to 0.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-20 point improvement on a 100 point scale SMD 0.5 to 0.8</td>
</tr>
<tr>
<td>Large</td>
<td>&gt;20 point improvement on a 100 point scale SMD &gt;0.8</td>
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Recommendation Grid

Adapted from the GRADE working group

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
<th>Benefits do or do not clearly outweigh risks</th>
<th>Benefits and risks and burdens are finely balanced</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Insufficient</td>
<td>Strong</td>
<td>I</td>
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</table>
### Interpretation: “Strong” recommendations

<table>
<thead>
<tr>
<th>Grade of recommendation/description</th>
<th>Benefit vs. Risk and burdens</th>
<th>Methodological Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs w/o important limitations or overwhelming evidence from observational studies</td>
<td>Can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Strong recommendation, moderate quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations or exceptionally strong evidence from observational studies</td>
<td>Can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Strong recommendation, low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>May change when higher quality evidence becomes available</td>
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</tbody>
</table>

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### Interpretation: “Weak” recommendations

<table>
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<tr>
<th>Grade of recommendation/description</th>
<th>Benefit vs. Risk and burdens</th>
<th>Methodological Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burdens</td>
<td>RCTs w/o important limitations or overwhelming evidence from observational studies</td>
<td>Best action may differ depending on circumstances or patient/societal values</td>
</tr>
<tr>
<td>Weak recommendation, moderate quality evidence</td>
<td>Benefits closely balanced with risks and burdens</td>
<td>RCTs with important limitations or exceptionally strong evidence from observational studies</td>
<td>Best action may differ depending on circumstances or patient/societal values</td>
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<tr>
<td>Very weak recommendation, low-quality evidence</td>
<td>Uncertainty in estimates of benefits, risks, and burdens</td>
<td>Observational studies or case series</td>
<td>Other alternatives may be reasonable</td>
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</table>

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