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| **Critique author** | Ed Whitney |

| **Bibliographic Data** | |
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| Authors | McNicol ED, Midbari A, Eisenberg E. |
| Title | Opioids for neuropathic pain. |
| PMID | 23986501 |
| Citation | Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006146. |
| Other information if relevant | |

| **Methods** | |
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| Aim of study | To assess the efficacy and safety of opioids in the setting of neuropathic pain |
| Design | Systematic review and meta-analysis of randomized clinical trials |

| **PICOS** | |
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| Population from which participants are drawn | - Patients with only neuropathic pain<br>- Studies of patients with both neuropathic and nociceptive pain were excluded if the results for the two types of pain were combined and not reported separately |
| Intervention being evaluated | - Opioids administered orally, transdermally, intravenously, intramuscularly, or subcutaneously<br>- Combination opioid preparations such as codeine with acetaminophen were excluded from the review<br>- Opioids administered intrathecally or epidurally were excluded from the review<br>- Tramadol and tapentadol were not considered to be pure opioids and these drugs were reviewed in a different Cochrane Review<br>- Buprenorphine was excluded because of being a partial mu receptor antagonist |

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| Comparison or control intervention | - Placebo<br>- Other opioids or different doses of the same opioid<br>- Other classes of drugs (such as antidepressants) for neuropathic pain |
| Outcomes | - Primary outcome was responder rates defined as percentages of participants whose pain intensity was reduced by 33% or by 50% from baseline<br>- Secondary outcomes were pain reduction on numerical scales, scores on quality of life instruments, incidence of adverse events on treatment, patient dropouts due to adverse events, and patient dropouts due to lack of efficacy |
| Study types | - Randomized controlled trials only<br>- Trials were divided into two categories according to duration: "short-term" trials which employed a single dose or IV infusion, and "intermediate term" trials which encompassed all other trials<br>- No trials were considered to be "long term" because no trial was sufficiently long to form a basis for conclusions about chronic administration of opioids |

| **Study selection** | |
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| Search date of literature review | October 24, 2012 |
| Databases in literature search | CENTRAL, MEDLINE, EMBASE |
| How authors assessed study quality (risk of bias and other considerations | Cochrane Risk of Bias tool for<br>- Random sequence generation<br>- Allocation concealment<br>- Blinding of participants and personnel delivering care<br>- Blinding of outcome assessment<br>- Incomplete outcome data (attrition and withdrawal from study)<br>- Selective outcome reporting |
| Additional information if relevant | - Study duration and methods of handling missing data were also considered as likely sources of bias |

| **Results** | |
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| Number of studies screened | - 8528 records were screened |

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| Number of studies selected for analysis of results | - 17 short-term studies<br>- 14 intermediate-term studies |
| Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc) | - Random effects models were used for all analyses in which data were pooled |
| Quality of studies as assessed by authors | - 15 of the 31 included studies had a low risk of bias for random sequence generation<br>- 10 studies had a low risk of bias for allocation concealment<br>- Only 5 of the 17 short term studies were adequately blinded<br>- 10 of the 14 intermediate-term studies were adequately blinded<br>- 13 of 17 short-term trials had a low risk of attrition bias<br>- Only 6 of the 14 intermediate term trials had a low risk of attrition bias<br>- The vast majority of trials had low risk of bias for selective outcome reporting |
| Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc) | - For short-term (mostly single-dose) studies, responder rates were not reported<br>- For intermediate-term studies, data were combined from 6 trials with 727 patients for the outcome of at least 33% pain relief, and estimated that opioids achieved this goal in 57% of patients versus 34% of placebo patients; the number needed to treat (NNT) to achieve one additional success was 4 patients<br>- For intermediate term studies which compared success rates for 50% or more pain relief in 305 patients, 47% of opioid and 30% of placebo patients achieved this goal, for NNT of 5.9<br>- The same success rates were estimated for studies of opioid versus gabapentin and for opioid versus nortriptyline, and in neither comparison was opioid superior to the other drug |

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| Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc) | - Data could be combined from four short-term studies (90 patients total) for pain intensity, with meta-analysis showing a difference of 16 points on a 100 point scale (95% CI 9 to 25 points) favoring opioid over placebo<br>- For the intermediate term studies, numerous secondary outcomes were compared<br>- Noteworthy among the secondary outcomes was the absence of clear opioid advantages over placebo for quality of life scores<br>- As expected, patients treated with opioids were more likely than those on placebo to experience constipation (34% versus 9%) and drowsiness (29% versus 14%), among other side effects |
| Additional information if relevant | |

| **Conclusions** | |
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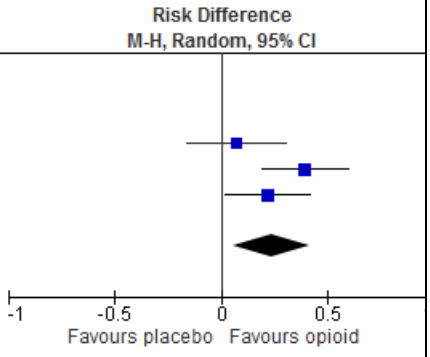
| Key conclusions of study authors | - Intermediate term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain in terms of likelihood of recording a 33% or a 50% reduction in pain intensity<br>- Similar benefits of opioids over placebo could not be shown for improvements in activities of daily life or quality of life<br>- Firm conclusions cannot be drawn concerning functional effects of opioids due to the inconsistency of reporting these outcomes<br>- Most of the study durations were brief (8 weeks or less)<br>- Many of the studies used statistical methods which are likely to be biased: reporting only on patients who complete the trial and using last observation carried forward as a method of imputation for missing data<br>- The use of a single dimension (pain response) for efficacy of opioids is problematic, since pain is a multidimensional phenomenon and there is considerable variety even within specific etiologies (such as postherpetic neuralgia) of chronic pain<br>- The dose ranges tested were in the low to intermediate range in the included studies, and there is no support for high doses of opioids for chronic pain<br>- Analgesic effects of opioids for neuropathic pain is subject to considerable uncertainty due to the potential for bias in the analysis of many studies |
| Additional information if relevant | |

**Comments by DOWC staff**

- In areas of active research, it is common practice for Cochrane reviews to provide references to studies awaiting assessment and, separately, to studies which are ongoing at the time of the writing of the review
- Neither ongoing studies nor studies awaiting assessment were referenced in this Cochrane review
- A search of PubMed on July 18,2016 for "neuropathic pain" AND "opioid treatment" did not turn up any studies comparing opioids versus placebo for noncancer neuropathic pain since October 2012 when the search was done
- The same PubMed search turned up one study of noncancer pain comparing pregabalin with tramadol; this Cochrane review excluded studies of tramadol, which is the subject of a separate Cochrane review
- This appears to represent the lack of new research concerning opioids for neuropathic pain
- At the beginning of the review, the authors label the "Publication status and date" as "Stable" with no update expected, reflecting the likely status of ongoing research as not very active
- The authors appear to come to a conclusion that opioids are more effective than placebo in the primary outcomes of 33% and 50% pain reduction, but then appear to downgrade their own conclusion by stating that the results of many studies could be biased by their methods for handling incomplete outcome data (such as using last observation carried forward)
- It is possible to reanalyze the data for 33% pain reduction in Analysis 2.1 on page 61 by removing three studies with an "unclear risk of bias" for missing data (Gilron 2005, Gimbel 2003, and Hanna 2008), keeping the three studies with a "low risk of bias" (Khoromi 2007, Watson 1998, and Wu 2008, and the result is nearly identical to the pooled risk difference for all six studies combined (0.24 versus 0.25)

| | Experimental | | Control | | | Risk Difference |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI |
| Gilron 2005 | 35 | 44 | 13 | 42 | 0.0% | 0.49 [0.30, 0.67] |
| Gimbel 2003 | 37 | 82 | 20 | 77 | 0.0% | 0.19 [0.05, 0.34] |
| Hanna 2008 | 68 | 121 | 52 | 127 | 0.0% | 0.15 [0.03, 0.28] |
| Khoromi 2007 | 13 | 32 | 11 | 33 | 30.0% | 0.07 [-0.16, 0.31] |
| Watson 1998 | 22 | 38 | 7 | 38 | 34.9% | 0.39 [0.20, 0.59] |
| Wu 2008 | 33 | 50 | 19 | 43 | 35.1% | 0.22 [0.02, 0.42] |
| **Total (95% CI)** | | **120** | | **114** | **100.0%** | **0.24 [0.06, 0.41]** |
| Total events | 68 | | 37 | | | |

Heterogeneity: Tau² = 0.01; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 2.60 (P = 0.009)




- Similarly, for Analysis 2.2 on page 62, where five studies were combined to calculate a pooled risk difference for the 50% pain reduction analysis, only one study (Huse 2001) is at an "unclear risk of bias;" the other four are rated at a "low risk of bias" and the pooled risk difference of 0.15 is practically identical to the result of 0.17
- Therefore, the authors' expressed concerns about the potential for bias arising from the handling of missing outcome data appear to be somewhat misplaced, and the effects of opioid versus placebo appear to be reasonably efficient for the primary outcomes when the effects of those bias are removed
- Some of the secondary outcomes in the Cochrane review are of primary outcome for a chronic pain guideline: function and quality of life improvements do not appear to reflect the benefits reported by the pain reduction scores

| **Assessment by DOWC staff** | |
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| Overall assessment as suitability of evidence for the guideline<br>☒ High quality<br>☐ Adequate<br>☐ Inadequate | The Cochrane review is of high quality, and provides good evidence for a statement that opioids are more efficient than placebo in reducing neuropathic pain by clinically significant amounts during the first 8 weeks of treatment. There is a lack of evidence that opioids improve function and quality of life more effectively than placebo. There is good evidence that opioids produce significantly more adverse effects than placebo such as constipation, drowsiness, dizziness, nausea, and vomiting. There is a lack of evidence that they are superior to gabapentin or nortriptyline for pain reduction |
| If inadequate, main reasons for recommending that the article not be cited as evidence | |

| **Additional references if relevant** |
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