Table 3a: The effect of opioid add-on therapy vs. optimization of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), for adult patients with chronic non-cancer pain (see [https://www.magicapp.org/public/guideline/8nyb0E/pico/jXNPbn/widget?openOnLoad=1](https://www.magicapp.org/public/guideline/8nyb0E/pico/jXNPbn/widget?openOnLoad=1))

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Absolute effect estimates (95% CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal side effects</td>
<td>RR 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 studies 1-5</td>
<td>Difference: 56 more per 1000 (CI 95% 20 more 116 more)</td>
<td>High</td>
<td>Opioid therapy results in a small increase in gastro intestinal side effects</td>
</tr>
<tr>
<td>Pain (10 cm VAS; lower is better)*</td>
<td>Based on data from 2,250 patients in 13 studies 1-3, 5-13</td>
<td>Difference: MD 0.49 lower (CI 95% 1.24 lower to 0.26 higher)</td>
<td>Low</td>
<td>Opioid therapy may result in little or no difference in pain compared to NSAIDS</td>
</tr>
<tr>
<td>Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)**</td>
<td>Based on data from 1,972 patients in 8 studies 2, 3, 5, 7, 8, 12-14</td>
<td>Difference: MD 1.5 lower (CI 95% 3.08 lower to 0.08 higher)</td>
<td>Moderate</td>
<td>Opioid therapy likely results in little or no difference in physical function compared to NSAIDS</td>
</tr>
<tr>
<td>Addiction follow-up not reported</td>
<td>Based on data from 22,278 patients in 9 studies 15-23</td>
<td>Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of addiction</td>
</tr>
<tr>
<td>Fatal Overdose median 2-6 years</td>
<td>Based on data from 285,520 patients in 1 study 24</td>
<td>Annual risk of fatal overdose is 0.10% with &lt;20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with &gt;100 mg MED/day</td>
<td>High</td>
<td>Opioid therapy results in a rare but important risk of fatal overdose</td>
</tr>
<tr>
<td>Non-fatal overdose 1 month to 10 years</td>
<td>Based on data from 9,940 patients in 1 study 25</td>
<td>Annual risk of non-fatal overdose is 0.2% with &lt;20mg MED/day 0.7% with 50-99mg MED/day 0.8% with &gt;100 mg MED/day</td>
<td>Moderate</td>
<td>Opioid therapy likely results in a small but important risk of non-fatal overdose</td>
</tr>
<tr>
<td>Diversion 1 year</td>
<td>Based on data from 472,200 patients in 1 study 26</td>
<td>Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of diversion</td>
</tr>
</tbody>
</table>

Legend
a: Two cited papers each reported on two individual studies, therefore seven individual trials were reported by five references
b: The magnitude of statistical heterogeneity was high, with I² = 94.5 %
c: Wide confidence intervals which include benefit and harm
d: Point estimates varied substantially, from 0.7% to 15.7%
e: Small number of events
f: Response rate of 66%. Outcome was self-reported
Table 3b: The effect of opioid add-on therapy vs. optimization of therapy with anticonvulsants, for adult patients with chronic non-cancer pain (https://www.magicapp.org/public/guideline/8nyb0E/pico/L6Kl0n/widget?openOnLoad=1)

<table>
<thead>
<tr>
<th>Outcome follow-up</th>
<th>Relative risk (95%CI) no. of patients and studies</th>
<th>Absolute effect estimates (95%CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (difference in patients who achieve the MID or greater)* 4 to 6 weeks</td>
<td>RR 1.26 (CI 95% 1.05 to 1.42) Based on data from 303 patients in 3 studies</td>
<td>618 per 1000</td>
<td>Difference: 161 more per 1000 (CI 95% 31 more to 260 more)</td>
<td>Low</td>
</tr>
<tr>
<td>Gastrointestinal side effects 4 to 6 weeks</td>
<td>RR 10.64 (CI 95% 2.01 to 56.24) Based on data from 303 patients in 3 studies</td>
<td>6 per 1000</td>
<td>Difference: 58 more per 1000 (CI 95% 6 more to 331 more)</td>
<td>Low</td>
</tr>
<tr>
<td>Pain (10 cm VAS; lower is better)* 4 to 6 weeks</td>
<td>Based on data from 303 patients in 3 studies</td>
<td>Difference: MD 0.9 lower (CI 95% 1.65 lower to 0.14 lower)</td>
<td>Low</td>
<td>Opioid therapy likely results in a small but important improvement in pain compared to anticonvulsants</td>
</tr>
<tr>
<td>Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)** 4 to 6 weeks</td>
<td>Based on data from 303 patients in 3 studies</td>
<td>Difference: MD 0.45 higher (CI 95% 5.77 lower to 6.66 higher)</td>
<td>Low</td>
<td>Opioids may result in little to no difference in physical function compared to anticonvulsants</td>
</tr>
<tr>
<td>Addiction follow-up not reported</td>
<td>Based on data from 22,278 patients in 9 studies</td>
<td>Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of addiction</td>
</tr>
<tr>
<td>Fatal overdose median 2.6 years</td>
<td>Based on data from 285,520 patients in 1 study</td>
<td>Annual risk of fatal overdose is 0.10% with &lt;20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with &gt;100 mg MED/day</td>
<td>High</td>
<td>Opioid therapy results in a rare but important risk of fatal overdose</td>
</tr>
<tr>
<td>Non-fatal overdose 1 month to 10 years</td>
<td>Based on data from 9,940 patients in 1 study</td>
<td>Annual risk of non-fatal overdose is 0.2% with &lt;20mg MED/day 0.7% with 50-99mg MED/day 0.8% with &gt;100 mg MED/day</td>
<td>Moderate</td>
<td>Opioid therapy likely results in a small but important risk of non-fatal overdose</td>
</tr>
<tr>
<td>Diversion 1 year</td>
<td>Based on data from 472,200 patients in 1 study</td>
<td>Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of diversion</td>
</tr>
</tbody>
</table>

Legend
a: Two out of three studies (Sakai et al. 2015, Ko et al. 2010) had no allocation concealment and no blinding  
b: Confidence interval includes both important benefit and no clinically meaningful effect

due to serious risk of bias, Due to serious imprecision

Due to serious risk of bias, Due to serious imprecision

Opioid therapy likely results in a small but important risk of diversion
c: Wide confidence intervals

d: Confidence interval includes both benefit and harm

e: Point estimates varied substantially, from 0.7% to 15.7%

f: Small number of events

g: Response rate of 66%. Outcome was self-reported

* Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm

** Minimally important difference for physical function on a 100-point SF-36 physical component summary score is an increase of 5 points

MD: mean difference. Gastrointestinal side effects include nausea, vomiting, and constipation.

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**Table 3c:** The effect of opioid add-on therapy vs. optimization of therapy with tricyclic antidepressants, for adult patients with chronic non-cancer pain


<table>
<thead>
<tr>
<th>Outcome follow-up</th>
<th>no. of patients and studies</th>
<th>Absolute effect estimates (95%CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (10 cm VAS; lower is better)*</td>
<td>Based on data from 183 patients in 3 studies</td>
<td><strong>Difference: MD 0.15 lower</strong> (CI 95% 1.04 lower to 0.74 higher)</td>
<td>Low</td>
<td>Opioids may result in little to no difference in pain compared to tricyclic antidepressants</td>
</tr>
<tr>
<td>Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)**</td>
<td>Based on data from 107 patients in 2 studies**</td>
<td><strong>Difference: MD 5.29 lower</strong> (CI 95% 13.7 lower to 3.12 higher)</td>
<td>Low</td>
<td>Opioids may result in little to no difference in physical function compared to tricyclic antidepressants</td>
</tr>
<tr>
<td>Addiction follow-up not reported</td>
<td>Based on data from 22,278 patients in 9 studies</td>
<td>Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of addiction</td>
</tr>
<tr>
<td>Fatal overdose median 2.6 years</td>
<td>Based on data from 285,520 patients in 1 study</td>
<td>Annual risk of fatal overdose is 0.10% with &lt;20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with &gt;100 mg MED/day</td>
<td>High</td>
<td>Opioid therapy results in a rare but important risk of fatal overdose</td>
</tr>
<tr>
<td>Non-fatal overdose 1 month to 10 years</td>
<td>Based on data from 9,940 patients in 1 study</td>
<td>Annual risk of non-fatal overdose is 0.2% with &lt;20mg MED/day 0.7% with 50-99mg MED/day 0.8% with &gt;100 mg MED/day</td>
<td>Moderate</td>
<td>Opioid therapy likely results in a small but important risk of non-fatal overdose</td>
</tr>
<tr>
<td>Diversion 1 year</td>
<td>Based on data from 472,200 patients in 1 study</td>
<td>Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013</td>
<td>Moderate</td>
<td>Opioid therapy likely results in an important risk of diversion</td>
</tr>
</tbody>
</table>

**Legend**

a: High loss to follow-up in all studies (>25%) 

b: Confidence interval includes benefit and harm

c: Point estimates varied substantially, from 0.7% to 15.7%

d: Small number of events

e: Response rate of 66%. Outcome was self-reported

* Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm

** Minimally important difference for physical function on a 100-point SF-36 physical component summary score is an increase of 5 points


**Table 3d**: The effect of opioid add-on therapy vs. optimization of therapy with nabilone, for adult patients with chronic non-cancer pain

(https://www.magicapp.org/public/guideline/8nyb0E/pico/jNB77j/widget?openOnLoad=1)

<table>
<thead>
<tr>
<th>Outcome follow-up</th>
<th>no. of patients and studies</th>
<th>Absolute effect estimates (95%CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (10 cm VAS; lower is better)* 6 weeks</td>
<td>Based on data from 73 patients in 1 study</td>
<td>Difference: MD 0.13 lower (CI 95%: 1.04 lower to 0.77 higher)</td>
<td>Low</td>
<td>Opioids may result in little to no difference in pain compared to nabilone</td>
</tr>
<tr>
<td>Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)** 6 weeks</td>
<td>Based on data from 71 patients in 1 study</td>
<td>Difference: MD 1.2 lower (CI 95%: 4.5 lower to 2.1 higher)</td>
<td>Low</td>
<td>Opioids may result in little to no difference in physical function compared to nabilone</td>
</tr>
</tbody>
</table>

**Legend**

a: Did not report randomization or allocation; loss to follow-up was 33%

b: Confidence interval includes benefit and harm

* Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm

** Minimally important difference for physical function on a 100-point SF-36 physical component summary score is an increase of 5 points

MD: mean difference

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**Table 3e**: The effect of opioid add-on therapy vs. optimization of therapy with mexiletine, for adult patients with chronic non-cancer pain

(https://www.magicapp.org/public/guideline/8nyb0E/pico/Ev1zan/widget?openOnLoad=1)

<table>
<thead>
<tr>
<th>Outcome follow-up</th>
<th>no. of patients and studies</th>
<th>Absolute effect estimates (95%CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (10 cm VAS; lower is better)* 2 months</td>
<td>Based on data from 60 patients in 1 study</td>
<td>Difference: MD 1.3 lower (CI 95%: 2.15 lower to 0.45 lower)</td>
<td>Moderate</td>
<td>Opioid therapy likely results in a small but important improvement in pain compared to mexiletine</td>
</tr>
</tbody>
</table>

**Legend**

a: Loss to follow-up was 42%

* Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm

MD: mean difference

---

<table>
<thead>
<tr>
<th>Outcome follow-up</th>
<th>Relative risk (95% CI) no. of studies (patients)</th>
<th>Absolute effect estimates (95% CI)</th>
<th>Quality of evidence</th>
<th>Plain Language Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (difference in patients who achieve the MID or greater)*</td>
<td>RR 1.25 (CI 95% 1.21 to 1.29) Based on data from 13,876 patients in 27 studies,5 34-59</td>
<td>448 per 1000 560 per 1000 Difference: 112 more per 1000 (CI 95% 94 more to 130 more)</td>
<td>High</td>
<td>Opioid add-on therapy results in a small but important increase in the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS compared with placebo.</td>
</tr>
<tr>
<td>Physical function (difference in patients who achieve the MID or greater)**</td>
<td>RR 1.24 (CI 95% 1.17 to 1.3) Based on data from 12,058 patients in 33 studies,5 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71</td>
<td>424 per 1000 526 per 1000 Difference: 102 more per 1000 (CI 95% 72 more to 127 more)</td>
<td>High</td>
<td>Opioid add-on therapy results in a small but important increase in the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.</td>
</tr>
<tr>
<td>Gastrointestinal side effects</td>
<td>RR 3.08 (CI 95% 2.53 to 3.75) Based on data from 14,449 patients in 36 studies,5 34-38, 40-44, 46-47, 51-55, 57, 59, 62-66, 69-79</td>
<td>28 per 1000 86 per 1000 Difference: 58 more per 1000 (CI 95% 43 more to 77 more)</td>
<td>High</td>
<td>Opioid add-on therapy results in an increase in gastrointestinal side effects</td>
</tr>
<tr>
<td>Pain (10 cm VAS; lower is better)</td>
<td>Based on data from: 13,876 patients in 27 studies,5 34-59</td>
<td>Difference: MD 0.64 lower (CI 95% 0.76 lower to 0.53 lower)</td>
<td>High</td>
<td>Opioid add-on therapy results in a small but important improvement in pain</td>
</tr>
<tr>
<td>Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)</td>
<td>Based on data from: 12,058 patients in 33 studies,5 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71</td>
<td>Difference: MD 2.16 higher (CI 95% 1.56 higher to 2.76 higher)</td>
<td>High</td>
<td>Opioid add-on therapy results in a small but important improvement in physical function</td>
</tr>
<tr>
<td>Addiction not reported</td>
<td>Based on data from 22,278 patients in 9 studies15-23</td>
<td>Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)</td>
<td>Moderate</td>
<td>Opioid add-on therapy likely results in an important risk of addiction</td>
</tr>
<tr>
<td>Fatal overdose median 2.6 years</td>
<td>Based on data from 285,520 patients in 1 study24</td>
<td>Annual risk of fatal overdose is 0.10% with &gt;20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with &gt;100 mg MED/day</td>
<td>High</td>
<td>Opioid add-on therapy results in a rare but important risk of fatal overdose</td>
</tr>
<tr>
<td>Non-fatal overdose 1 to 119 months</td>
<td>Based on data from 9,940 patients in 1 study25</td>
<td>Annual risk of non-fatal overdose is 0.2% with &lt;20mg MED/day 0.7% with 50-99mg MED/day 0.8% with &gt;100 mg MED/day</td>
<td>Moderate</td>
<td>Opioid add-on therapy likely results in a small but important increase in the risk of non-fatal overdose</td>
</tr>
<tr>
<td>Diversion</td>
<td>Based on data from Among US adults, the prevalence of opioid therapy likely</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3f: The effect of opioid add-on therapy, vs. continued non-opioid therapy, for adult patients with chronic non-cancer pain, without current or past substance use disorder and without other current active psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain (https://www.magicapp.org/public/guideline/8nyb0E/pico/Lrbwj/widget?openOnLoad=1)
12 months | 472,200 patients in 1 study\textsuperscript{36} | nonmedical use of prescription opioids was 4.9% (95% CI, 4.6% to 5.2%) in 2013 | Due to serious risk of bias\textsuperscript{c} | results in an important risk of diversion

**Legend**
- a: Point estimates varied substantially, from 0.7% to 15.7%
- b: Small number of events
- c: Response rate of 66%. Outcome was self-reported

* Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
** Minimally important difference for physical function on a 100-point short form-36 (SF-36) physical component summary score is an increase of 5-points.

MD: mean difference. Gastrointestinal side effects include nausea, vomiting, and constipation
References


