

### Appendix 3 (as supplied by the authors): Supplementary Tables 3a–3f

**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>)

Outcome Follow-up	Relative risk (95%CI) no. of patients and studies	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		NSAIDs	Opioids		
<b>Gastrointestinal side effects</b>  6 to 26 weeks	RR 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 <sup>a</sup> studies <sup>1-5</sup>	<b>37 per 1000</b>	<b>93 per 1000</b>  <b>Difference: 56 more per 1000</b> (CI 95% 20 more 116 more)	<b>High</b>	Opioid therapy results in a small increase in gastrointestinal side effects
<b>Pain</b> (10 cm VAS; lower is better)*  1 to 6 months	Based on data from 2,250 patients in 13 studies <sup>1-3, 5-13</sup>	<b>Difference: MD 0.49 lower</b> (CI 95% 1.24 lower to 0.26 higher)		<b>Low</b> Due to serious inconsistency <sup>b</sup> , Due to serious imprecision <sup>c</sup>	Opioid therapy may result in little or no difference in pain compared to NSAIDS
<b>Physical function</b> (0 to 100-point SF-36 physical component summary scale; higher is better)**  1 to 4 months	Based on data from 1,972 patients in 8 studies <sup>2, 3, 5, 7, 8, 12-14</sup>	<b>Difference: MD 1.5 lower</b> (CI 95% 3.08 lower to 0.08 higher)		<b>Moderate</b> Due to serious imprecision <sup>c</sup>	Opioid therapy likely results in little or no difference in physical function compared to NSAIDS
<b>Addiction</b>  follow-up not reported	Based on data from 22,278 patients in 9 studies <sup>15-23</sup>	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		<b>Moderate</b> Due to serious inconsistency <sup>d</sup>	Opioid therapy likely results in an important risk of addiction
<b>Fatal Overdose</b>  median 2-6 years	Based on data from 285,520 patients in 1 study <sup>24</sup>	Annual risk of fatal overdose is 0.10% with <20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with >100 mg MED/day		<b>High</b>	Opioid therapy results in a rare but important risk of fatal overdose
<b>Non-fatal overdose</b>  1 month to 10 years	Based on data from 9,940 patients in 1 study <sup>25</sup>	Annual risk of non-fatal overdose is 0.2% with <20mg MED/day 0.7% with 50-99mg MED/day 0.8% with >100 mg MED/day		<b>Moderate</b> Due to serious imprecision <sup>c</sup>	Opioid therapy likely results in a small but important risk of non- fatal overdose
<b>Diversion</b>  1 year	Based on data from 472,200 patients in 1 study <sup>26</sup>	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%- 5.22%) in 2013.		<b>Moderate</b> Due to serious risk of bias <sup>f</sup>	Opioid therapy likely results in an important risk of diversion

#### 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  $I^2 = 94.5\%$
- 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

\* 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

**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/L6K10n/widget?openOnLoad=1>)

Outcome follow-up	Relative risk (95%CI) no. of patients and studies	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		Anticonvulsants	Opioids		
<b>Pain</b> (difference in patients who achieve the MID or greater)*  4 to 6 weeks	RR 1.26 (CI 95% 1.05 to 1.42) Based on data from 303 patients in 3 studies <sup>27-29</sup>	<b>618 per 1000</b>	<b>779 per 1000</b>  <b>Difference: 161 more per 1000</b> (CI 95% 31 more to 260 more)	<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioid therapy may result in a large increase in the proportion of patients who achieve a 1 cm reduction on a 10-cm VAS compared to anticonvulsants
<b>Gastrointestinal side effects</b>  4 to 6 weeks	RR 10.64 (CI 95% 2.01 to 56.24) Based on data from 303 patients in 3 studies <sup>27-29</sup>	<b>6 per 1000</b>	<b>64 per 1000</b>  <b>Difference: 58 more per 1000</b> (CI 95% 6 more to 331 more)	<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>c</sup>	Opioid therapy may result in an increase in gastrointestinal side effects compared to anticonvulsants
<b>Pain</b> (10 cm VAS; lower is better)*  4 to 6 weeks	Based on data from 303 patients in 3 studies <sup>27-29</sup>	<b>Difference: MD 0.9 lower</b> (CI 95% 1.65 lower to 0.14 lower)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioid therapy may result in a small but important improvement in pain compared to anticonvulsants
<b>Physical function</b> (0 to 100-point SF-36 physical component summary scale; higher is better)**  4 to 6 weeks	Based on data from 303 patients in 3 studies <sup>27-29</sup>	<b>Difference: MD 0.45 higher</b> (CI 95% 5.77 lower to 6.66 higher)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>d</sup>	Opioids may result in little to no difference in physical function compared to anticonvulsants
<b>Addiction</b>  follow-up not reported	Based on data from 22,278 patients in 9 studies <sup>15-23</sup>	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		<b>Moderate</b> Due to serious inconsistency <sup>e</sup>	Opioid therapy likely results in an important risk of addiction
<b>Fatal overdose</b>  median 2.6 years	Based on data from 285,520 patients in 1 study <sup>24</sup>	Annual risk of fatal overdose is 0.10% with <20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with >100 mg MED/day		<b>High</b>	Opioid therapy results in a rare but important risk of fatal overdose
<b>Non-fatal overdose</b>  1 month to 10 years	Based on data from 9,940 patients in 1 study <sup>25</sup>	Annual risk of non-fatal overdose is 0.2% with <20mg MED/day 0.7% with 50-99mg MED/day 0.8% with >100 mg MED/day		<b>Moderate</b> Due to serious imprecision <sup>f</sup>	Opioid therapy likely results in a small but important risk of non-fatal overdose
<b>Diversion</b>  1 year	Based on data from 472,200 patients in 1 study <sup>26</sup>	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013		<b>Moderate</b> Due to serious risk of bias <sup>g</sup>	Opioid therapy likely results in an important risk of diversion

**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

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.

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

(<https://www.magicapp.org/public/guideline/8nyb0E/pico/EdV6zL/widget?openOnLoad=1>)

Outcome follow-up	no. of patients and studies	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		Antidepressants	Opioids		
<b>Pain</b> (10 cm VAS; lower is better)*  5 to 8 weeks	Based on data from 183 patients in 3 studies	<b>Difference: MD 0.15 lower</b> (CI 95% 1.04 lower to 0.74 higher)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioids may result in little to no difference in pain compared to tricyclic antidepressants
<b>Physical function</b> (0 to 100-point SF-36 physical component summary scale; higher is better)**  5 to 6 weeks	Based on data from 107 patients in 2 studies <sup>30,31</sup>	<b>Difference: MD 5.29 lower</b> (CI 95% 13.7 lower to 3.12 higher)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioids may result in little to no difference in physical function compared to tricyclic antidepressants
<b>Addiction</b>  follow-up not reported	Based on data from 22,278 patients in 9 studies 22,278 patients in 9 studies <sup>15-23</sup>	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		<b>Moderate</b> Due to serious inconsistency <sup>c</sup>	Opioid therapy likely results in an important risk of addiction
<b>Fatal overdose</b>  median 2.6 years	Based on data from 285,520 patients in 1 study <sup>24</sup>	Annual risk of fatal overdose is 0.10% with <20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with >100 mg MED/day		<b>High</b>	Opioid therapy results in a rare but important risk of fatal overdose
<b>Non-fatal overdose</b>  1 month to 10 years	Based on data from 9,940 patients in 1 study <sup>25</sup>	Annual risk of non-fatal overdose is 0.2% with <20mg MED/day 0.7% with 50-99mg MED/day 0.8% with >100 mg MED/day		<b>Moderate</b> Due to serious imprecision <sup>d</sup>	Opioid therapy likely results in a small but important risk of non-fatal overdose
<b>Diversion</b>  1 year	Based on data from 472,200 patients in 1 study <sup>26</sup>	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013		<b>Moderate</b> Due to serious risk of bias <sup>e</sup>	Opioid therapy likely results in an important risk of diversion

**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

MD: mean difference

**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>)

Outcome follow-up	no. of patients and studies	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		Trial of opioids	Nabilone		
<b>Pain</b> (10 cm VAS; lower is better)* 6 weeks	Based on data from 73 patients in 1 study <sup>32</sup>	<b>Difference: MD 0.13 lower</b> (CI 95% 1.04 lower to 0.77 higher)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioids may result in little to no difference in pain compared to nabilone
<b>Physical function</b> (0 to 100-point SF-36 physical component summary scale; higher is better)** 6 weeks	Based on data from 71 patients in 1 study <sup>32</sup>	<b>Difference: MD 1.2 lower</b> (CI 95% 4.5 lower to 2.1 higher)		<b>Low</b> Due to serious risk of bias <sup>a</sup> , Due to serious imprecision <sup>b</sup>	Opioids may result in little to no difference in physical function compared to nabilone

**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

**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>)

Outcome follow-up	no. of patients and studies	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		Mexiletine	Trial of opioids		
<b>Pain</b> (10 cm VAS; lower is better)* 2 months	Based on data from 60 patients in 1 study <sup>33</sup>	<b>Difference: MD 1.3 lower</b> (CI 95% 2.15 lower to 0.45 lower)		<b>Moderate</b> Due to serious risk of bias <sup>a</sup>	Opioid therapy likely results in a small but important improvement in pain compared to mexiletine

**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 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/Lrqbwj/widget?openOnLoad=1>)

Outcome follow-up	Relative risk (95%CI) no. of studies (patients)	Absolute effect estimates (95%CI)		Quality of evidence	Plain Language Summary
		continuing established therapy without opioids	opioid therapy		
<b>Pain</b> (difference in patients who achieve the MID or greater)*  3 to 6 months	RR 1.25 (CI 95% 1.21 to 1.29) Based on data from 13,876 patients in 27 studies <sup>5, 34-59</sup>	<b>448 per 1000</b>	<b>560 per 1000</b>	<b>High</b>	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
<b>Physical function</b> (difference in patients who achieve the MID or greater)**  1 to 6 months	RR 1.24 (CI 95% 1.17 to 1.3) Based on data from 12,058 patients in 33 studies <sup>5, 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71</sup>	<b>424 per 1000</b>	<b>526 per 1000</b>	<b>High</b>	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.
<b>Gastrointestinal side effects</b>  1 to 6 months	RR 3.08 (CI 95% 2.53 to 3.75) Based on data from 14,449 patients in 36 studies <sup>5, 34-38, 40-44, 46, 47, 51-55, 57, 59, 62-66, 69-79</sup>	<b>28 per 1000</b>	<b>86 per 1000</b>	<b>High</b>	Opioid add-on therapy results in an increase in gastrointestinal side effects
<b>Pain</b> (10 cm VAS; lower is better)  3 to 6 months	Based on data from: 13,876 patients in 27 studies <sup>5, 34-59</sup>	<b>Difference: MD 0.64 lower</b> (CI 95% 0.76 lower to 0.53 lower)		<b>High</b>	Opioid add-on therapy results in a small but important improvement in pain
<b>Physical function</b> (0 to 100-point SF-36 physical component summary scale; higher is better)  1 to 6 months	Based on data from: 12,058 patients in 33 studies <sup>5, 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71</sup>	<b>Difference: MD 2.16 higher</b> (CI 95% 1.56 higher to 2.76 higher)		<b>High</b>	Opioid add-on therapy results in a small but important improvement in physical function
<b>Addiction</b>  not reported	Based on data from 22,278 patients in 9 studies <sup>15-23</sup>	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		<b>Moderate</b> Due to serious inconsistency <sup>a</sup>	Opioid add-on therapy likely results in an important risk of addiction
<b>Fatal overdose</b>  median 2.6 years	Based on data from 285,520 patients in 1 study <sup>24</sup>	Annual risk of fatal overdose is 0.10% with <20mg MED/day 0.14% with 20-49mg MED/day 0.18% with 50-99mg MED/day 0.23% with >100 mg MED/day		<b>High</b>	Opioid add-on therapy results in a rare but important risk of fatal overdose
<b>Non-fatal overdose</b>  1 to 119 months	Based on data from 9,940 patients in 1 study <sup>25</sup>	Annual risk of non-fatal overdose is 0.2% with <20mg MED/day 0.7% with 50-99mg MED/day 0.8% with >100 mg MED/day		<b>Moderate</b> Due to serious imprecision <sup>b</sup>	Opioid add-on therapy likely results in a small but important increase in the risk of non-fatal overdose
<b>Diversion</b>	Based on data from	Among US adults, the prevalence of		<b>Moderate</b>	Opioid therapy likely

12 months	472,200 patients in 1 study <sup>26</sup>	nonmedical use of prescription opioids was 4.9% (95% CI, 4.6% to 5.2%) in 2013	Due to serious risk of bias <sup>c</sup>	results in an important risk of diversion
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**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

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