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)** NSAIDs Opioids	**Quality of evidence**	**Plain Language Summary**
Gastrointestinal side effects 6 to 26 weeks	RR 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7[a] studies [1-5]	**37 per 1000** **93 per 1000** **Difference: 56 more per 1000** (CI 95% 20 more 116 more)	**High**	Opioid therapy results in a small increase in gastrointestinal side effects
Pain (10 cm VAS; lower is better)* 1 to 6 months	Based on data from 2,250 patients in 13 studies[1-3, 5-13]	**Difference: MD 0.49 lower** (CI 95% 1.24 lower to 0.26 higher)	**Low** Due to serious inconsistency[b], Due to serious imprecision[c]	Opioid therapy may result in little or no difference in pain compared to NSAIDS
Physical function (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 [2, 3, 5, 7, 8, 12-14]	**Difference: MD 1.5 lower** (CI 95% 3.08 lower to 0.08 higher)	**Moderate** Due to serious imprecision[c]	Opioid therapy likely results in little or no difference in physical function compared to NSAIDS
Addiction follow-up not reported	Based on data from 22,278 patients in 9 studies[15-23]	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)	**Moderate** Due to serious inconsistency[d]	Opioid therapy likely results in an important risk of addiction
Fatal Overdose median 2-6 years	Based on data from 285,520 patients in 1 study[24]	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	**High**	Opioid therapy results in a rare but important risk of fatal overdose
Non-fatal overdose 1 month to 10 years	Based on data from 9,940 patients in 1 study[25]	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	**Moderate** Due to serious imprecision[e]	Opioid therapy likely results in a small but important risk of non-fatal overdose
Diversion 1 year	Based on data from 472,200 patients in 1 study[26]	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias[f]	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/L6Kl0n/widget?openOnLoad=1)

Outcome follow-up	**Relative risk (95%CI)** no. of patients and studies	**Absolute effect estimates (95%CI)** Anticonvulsants	Opioids	**Quality of evidence**	**Plain Language Summary**
Pain (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[27-29]	**618 per 1000**	**779 per 1000** **Difference: 161 more per 1000** (CI 95% 31 more to 260 more)	**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	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
Gastrointestinal side effects 4 to 6 weeks	RR 10.64 (CI 95% 2.01 to 56.24) Based on data from 303 patients in 3 studies[27-29]	**6 per 1000**	**64 per 1000** **Difference: 58 more per 1000** (CI 95% 6 more to 331 more)	**Low** Due to serious risk of bias[a], Due to serious imprecision[c]	Opioid therapy may result in an increase in gastrointestinal side effects compared to anticonvulsants
Pain (10 cm VAS; lower is better)* 4 to 6 weeks	Based on data from 303 patients in 3 studies[27-29]	**Difference: MD 0.9 lower** (CI 95% 1.65 lower to 0.14 lower)		**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	Opioid therapy may result in a small but important improvement in pain compared to anticonvulsants
Physical function (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[27-29]	**Difference: MD 0.45 higher** (CI 95% 5.77 lower to 6.66 higher)		**Low** Due to serious risk of bias[a], Due to serious imprecision[d]	Opioids may result in little to no difference in physical function compared to anticonvulsants
Addiction follow-up not reported	Based on data from 22,278 patients in 9 studies[15-23]	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		**Moderate** Due to serious inconsistency[e]	Opioid therapy likely results in an important risk of addiction
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 study[24]	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		**High**	Opioid therapy results in a rare but important risk of fatal overdose
Non-fatal overdose 1 month to 10 years	Based on data from 9,940 patients in 1 study[25]	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		**Moderate** Due to serious imprecision[f]	Opioid therapy likely results in a small but important risk of non-fatal overdose
Diversion 1 year	Based on data from 472,200 patients in 1 study[26]	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013		**Moderate** Due to serious risk of bias[g]	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)** Antidepressants Opioids	**Quality of evidence**	**Plain Language Summary**
Pain (10 cm VAS; lower is better)* 5 to 8 weeks	Based on data from 183 patients in 3 studies	**Difference: MD 0.15 lower** (CI 95% 1.04 lower to 0.74 higher)	**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	Opioids may result in little to no difference in pain compared to tricyclic antidepressants
Physical function (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[30, 31]	**Difference: MD 5.29 lower** (CI 95% 13.7 lower to 3.12 higher)	**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	Opioids may result in little to no difference in physical function compared to tricyclic antidepressants
Addiction follow-up not reported	Based on data from 22,278 patients in 9 studies 22,278 patients in 9 studies[15-23]	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)	**Moderate** Due to serious inconsistency[c]	Opioid therapy likely results in an important risk of addiction
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 study[24]	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	**High**	Opioid therapy results in a rare but important risk of fatal overdose
Non-fatal overdose 1 month to 10 years	Based on data from 9,940 patients in 1 study[25]	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	**Moderate** Due to serious imprecision[d]	Opioid therapy likely results in a small but important risk of non-fatal overdose
Diversion 1 year	Based on data from 472,200 patients in 1 study[26]	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58% to 5.22%) in 2013	**Moderate** Due to serious risk of bias[e]	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)** Trial of opioids Nabilone	**Quality of evidence**	**Plain Language Summary**
Pain (10 cm VAS; lower is better)* 6 weeks	Based on data from 73 patients in 1 study[32]	**Difference: MD 0.13 lower** (CI 95% 1.04 lower to 0.77 higher)	**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	Opioids may result in little to no difference in pain compared to nabilone
Physical function (0 to 100-point SF-36 physical component summary scale; higher is better)** 6 weeks	Based on data from 71 patients in 1 study[32]	**Difference: MD 1.2 lower** (CI 95% 4.5 lower to 2.1 higher)	**Low** Due to serious risk of bias[a], Due to serious imprecision[b]	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)** Mexiletine Trial of opioids	**Quality of evidence**	**Plain Language Summary**
Pain (10 cm VAS; lower is better)* 2 months	Based on data from 60 patients in 1 study[33]	**Difference: MD 1.3 lower** (CI 95% 2.15 lower to 0.45 lower	**Moderate** Due to serious risk of bias[a]	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)** continuing established therapy without opioids	 opioid therapy	**Quality of evidence**	**Plain Language Summary**
Pain (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[5, 34-59]	**448 per 1000**	**560 per 1000** **Difference: 112 more per 1000** (CI 95% 94 more to 130 more)	**High**	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
Physical function (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.[5, 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71]	**424 per 1000**	**526 per 1000** **Difference: 102 more per 1000** (CI 95% 72 more to 127 more)	**High**	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.
Gastrointestinal side effects 1 to 6 months	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]	**28 per 1000**	**86 per 1000** **Difference: 58 more per 1000** (CI 95% 43 more to 77 more)	**High**	Opioid add-on therapy results in an increase in gastrointestinal side effects
Pain (10 cm VAS; lower is better) 3 to 6 months	Based on data from: 13,876 patients in 27 studies.[5, 34-59]	**Difference: MD 0.64 lower** (CI 95% 0.76 lower to 0.53 lower)		**High**	Opioid add-on therapy results in a small but important improvement in pain
Physical function (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.[5, 27, 34-36, 38, 39, 41, 42, 44-48, 50, 51, 53, 55-57, 59-71]	**Difference: MD 2.16 higher** (CI 95% 1.56 higher to 2.76 higher)		**High**	Opioid add-on therapy results in a small but important improvement in physical function
Addiction not reported	Based on data from 22,278 patients in 9 studies[15-23]	Risk of opioid addiction is 5.5% (95% CI 3.91 to 7.03%)		**Moderate** Due to serious inconsistency[a]	Opioid add-on therapy likely results in an important risk of addiction
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 study[24]	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		**High**	Opioid add-on therapy results in a rare but important risk of fatal overdose
Non-fatal overdose 1 to 119 months	Based on data from 9,940 patients in 1 study[25]	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		**Moderate** Due to serious imprecision[b]	Opioid add-on therapy likely results in a small but important increase in the risk of non-fatal overdose
Diversion	Based on data from	Among US adults, the prevalence of		**Moderate**	Opioid therapy likely

12 months	472,200 patients in 1 study[26]	nonmedical use of prescription opioids was 4.9% (95% CI, 4.6% to 5.2%) in 2013	Due to serious risk of bias[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

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