The 2017 Draft Recommendations for Use of Opioids in Chronic Non-Cancer Pain

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Disclaimer

The draft recommendations in this guideline are presented to encourage public review and comment. The direction ('for' or 'against') and strength ('weak' or 'strong') of each recommendation has been established by a 15-member guideline panel of clinicians, methodologists and patients, and are unlikely to change unless compelling evidence emerges that was not considered by the panel. All feedback received regarding the wording of recommendations and associated text, and/or important considerations (please see Feedback Form), will be carefully considered by the guideline steering committee and used to inform the drafting of the final guideline document.

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Sections

Summary of recommendations

1 - Initiation and Dosing of Opioids in Patients with Chronic Non-Cancer Pain

Recommendation #1

When considering first-line therapy for patients with chronic non-cancer pain

Strong Recommendation AGAINST

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Recommendation #2

Patients with persistent problematic pain despite optimized non-opioid therapy, without current or past substance use disorder or current serious psychiatric disorder

Weak Recommendation

We suggest a trial of opioids rather than continued non-opioid therapy

By a trial of opioids, we mean initiation, titration, and diligent monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved

Recommendation #3

Patients with an active substance use disorder and chronic non-cancer pain

Strong Recommendation AGAINST

We recommend against the use of opioids

Clinicians should, if not yet addressed, facilitate treatment of the underlying substance use disorders

Recommendation #4

Patients with a current serious psychiatric disorder whose non-opioid therapy has been optimized, and who still experience persistent problematic pain (REC #4)

Weak Recommendation

We suggest stabilization of the psychiatric disorder before considering a trial of opioids

Recommendation #5

Patients with a history of substance use disorder, whose non-opioid therapy has been optimized, and who still experience persistent problematic pain

Weak Recommendation

We suggest continuing non-opioid therapy rather than a trial of opioids

Recommendation #6

Patients with chronic non-cancer pain beginning long term opioid therapy

Weak Recommendation

We suggest restricting the prescribed dose to under 50mg morphine equivalents daily ,rather than a dose of 50 to below 90 mg

The weak recommendation to restrict the prescribed dose to under 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose over 50mg to potentially achieve improved pain control

Recommendation #7

Strong Recommendation

We recommend restricting the prescribed dose to under 90mg morphine equivalents daily rather than no upper, or a higher limit on dosing

Some patients may gain important benefit over 90mg morphine equivalents, but not on lower doses. Referral to a colleague for a second opinion regarding the possibility of increasing above 90mg morphine equivalents daily may therefore be warranted in some individuals

2 - Rotation and Tapering of Opioids, for Patients with Chronic Non-Cancer Pain

Recommendation #8

For patients currently using 90 mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Recommendation #9

For patients currently using 90 mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects

Weak Recommendation

We suggest tapering opioids to the lowest possible dose, including discontinuation, rather than no change in opioid therapy

Some patients are likely to experience significant increase in pain or decrease in function that persist more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Recommendation #10

Patients using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary opioids reduction program

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration including several health professionals (possibilities include, but are not limited to, a primary care physician, a pharmacist, a physical therapist, a kinesiologist, a psychiatrist, and a psychologist).

1 - Initiation and Dosing of Opioids in Patients with Chronic Non-Cancer Pain

Recommendation #1

When considering first-line therapy for patients with chronic non-cancer pain

Strong Recommendation | AGAINST

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Rationale

Opioids, when added to non-opioids achieve, on average, modest improvements in pain and function at the cost of very frequent dependence, frequent addiction, and rare non-fatal unintentional overdose and death. A variety of non-opioid therapies as first-line treatment for patients with chronic non-cancer pain achieve a similar magnitude of improvement in pain and function but without the problems of dependence, addiction, and non-fatal overdose

Clinical Question/ PICO

Population: PICO 1a) Patients with chronic non-cancer pain considering first line therapy for pain

Intervention: Trial of opioids.

Comparator: Optimization of therapy with NSAIDs.

Summary

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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with NSAIDs.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects	Relative risk 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 studies. (Randomized controlled) Follow up 6-26 weeks	**37** per 1000	**93** per 1000 Difference: **56 more** per 1000 (CI 95% 20 more - 116 more)	**High**	Opioid therapy slightly worsens gastrointestinal side effects compared to NSAIDS
Pain	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 2,250 patients in 13 studies. (Randomized controlled) Follow up 1-6 months	cm (n/a)	cm (n/a) Difference: **MD 0.49 fewer** (CI 95% 1.24 fewer - 0.26 more)	**Low** Due to serious inconsistency, Due to serious imprecision	Opioid therapy may have little or no difference on pain compared to NSAIDS

Physical Function	Measured by: SF-36 Scale: 0-100 High better Based on data from: 1,972 patients in 8 studies. (Randomized controlled) Follow up 4-16 weeks	(n/a) (n/a) Difference: **MD 1.5 fewer** (CI 95% 3.08 fewer - 0.08 more)	**Moderate** Due to serious imprecision	Opioid therapy may have little or no difference on physical function compared to NSAIDS
Addiction	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy increases the risk of addiction
Fatal Overdose	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy increases the risk of fatal overdose
Non-fatal overdose	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy increases the risk of non-fatal overdose.
Diversion	Based on data from 472,200 patients in 1 studies	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.	Opioid therapy probably increases the risk of diversion

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: Serious** The magnitude of statistical heterogeneity was high, with I^2: 94.5 %. ; **Indirectness: No serious** **Imprecision: Serious** Wide confidence intervals which include benefit and harm ; **Publication bias: No serious**
Physical Function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious**

	reference used for intervention	**Imprecision: Serious** Wide confidence intervals include both benefit and harm ; **Publication bias: No serious**
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7% to 15.7% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal Overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** The study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State. ; **Imprecision: Serious** Small number of events. ; **Publication bias: No serious**
Diversion	**Intervention reference:** Systematic review	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Clinical Question/ PICO

Population: 1b) Patients with chronic non-cancer pain considering first line therapy for pain
Intervention: Trial of opioids.
Comparator: Optimization of therapy with anticonvulsants.

Summary

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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with anticonvulsants.	**Absolute effect estimates** Trial of opioids.	**Certainty in effect estimates**	**Summary**

			(Quality of evidence)	
Gastrointestinal side effects 5 Important	Relative risk 10.64 (CI 95% 2.01 - 56.24) Based on data from 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	**6** per 1000 — **64** per 1000 Difference: **58 more** per 1000 (CI 95% 6 more - 331 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may increase gastrointestinal side effects compared to anticonvulsants.
Pain (difference in patients who achieve the MID or greater) 9 Critical	Relative risk 1.26 (CI 95% 1.05 - 1.42) Based on data from 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	**618** per 1000 — **779** per 1000 Difference: **161 more** per 1000 (CI 95% 31 more - 260 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may increase the proportion of patients who achieve a 1 cm reduction on a 10-cm VAS compared to anticonvulsants.
Pain 9 Critical	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	cm (n/a) — cm (n/a) Difference: **MD 0.9 fewer** (CI 95% 1.65 fewer - 0.14 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may improve pain slightly compared to anticonvulsants.
Physical Function 9 Critical	Measured by: SF-36 Scale: 0-100 High better Based on data from: 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	(n/a) — (n/a) Difference: **MD 0.45 more** (CI 95% 5.77 fewer - 6.66 more)	**Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether opioid therapy improves or worsens physical function compared to anticonvulsants.
Addiction 9 Critical	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy increases the risk of addiction
Fatal overdose 9 Critical	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy increases the risk of fatal overdose.
Non-fatal overdose 9 Critical	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy increases the risk of non-fatal overdose.

Diversion 9 Critical	Based on data from 472,200 patients in 1 studies	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.	Opioid therapy probably increases the risk of diversion.
Details about studies used and certainty down- and upgrading				
Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (Sakai 2015, Ko 2010) had no allocation concealment and no blinding. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**		
Pain (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (sakai 2015, Ko 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2=71 %. ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both important benefit and no clinically meaningful effect ; **Publication bias: No serious**		
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (sakai 2015, Ko 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2=71 %. ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both important benefit and no clinically meaningful effect ; **Publication bias: No serious**		
Physical Function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (sakai 2015, Ko 2010) had no allocation concealment and no blinding. ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2:67 %. ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both benefit and harm ; **Publication bias: No serious**		
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7% to 15.7%. ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**		
Fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ;		

		Imprecision: No serious **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State ; **Imprecision: Serious** Small number of events and no confidence interval provided. ; **Publication bias: No serious**
Diversion	**Intervention reference:** Systematic review	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Clinical Question/ PICO

Population: 1c) Patients with chronic non-cancer pain considering first line therapy for pain

Intervention: Trial of opioids.

Comparator: Optimization of therapy with tricyclic antidepressants.

Summary

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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with tricyclic antidepressants. Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 9 Critical	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 183 patients in 3 studies. (Randomized controlled) Follow up 5-8 weeks	cm (n/a) cm (n/a) Difference: **MD 0.15 fewer** (CI 95% 1.04 fewer - 0.74 more)	**Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether opioid therapy improves or worsens pain compared to antidepressants.
Physical Function	Measured by: SF-36 Scale: 0-100 High better Based on data from: 107 patients in 2 studies. (Randomized controlled) Follow up 5-6 weeks	(n/a) (n/a) Difference: **MD 5.29 fewer** (CI 95% 13.7 fewer - 3.12 more)	**Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether opioid therapy improves or worsens physical function compared to antidepressants.

Addiction 9 Critical	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy increases the risk of addiction.
Fatal overdose 9 Critical	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy increases the risk of fatal overdose.
Non-fatal overdose 9 Critical	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy increases the risk of non-fatal overdose.
Diversion 9 Critical	Based on data from 472,200 patients in 1 studies	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.	Opioid therapy probably increases the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** High loss to follow up in all studies (>25%) ; **Inconsistency: No serious** **Indirectness: No serious** Follow up time is short, max 6 weeks ; **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**
Physical Function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** High loss to follow up in all studies (>25%) ; **Inconsistency: No serious** **Indirectness: No serious** Follow up time is short, max 6 weeks ; **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7%-15.7% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ;

		Imprecision: No serious **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was Group Health Cooperative, which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State. ; **Imprecision: Serious** Small number of events and no confidence interval provided. ; **Publication bias: No serious**
Diversion	**Intervention reference:** Systematic review	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Recommendation #2

Patients with persistent problematic pain despite optimized non-opioid therapy, without current or past substance use disorder or current serious psychiatric disorder

Weak Recommendation

We suggest a trial of opioids rather than continued non-opioid therapy

By a trial of opioids, we mean initiation, titration, and diligent monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved

Rationale

Opioids, when added to non-opioids achieve, on average, modest improvements in pain and function. Adverse effects include relatively frequent constipation, nausea and vomiting, cognitive changes, dependence, and addiction, and rare death and non-fatal unintentional overdose.

Clinical Question/ PICO

Population: PICO 2: Patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain

Intervention: Trial of opioids.

Comparator: Continue established therapy without opioids.

Summary

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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 4-26 weeks 9 Critical	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Opioid therapy worsens gastrointestinal side effects
Pain (difference in patients who achieve the MID or greater) 9 Critical	Relative risk 1.29 (CI 95% 1.24 - 1.34) Based on data from 13,948 patients in 35 studies. (Randomized controlled) Follow up 12-24 weeks	**424** per 1000	**547** per 1000 Difference: **123 more** per 1000 (CI 95% 102 more - 144 more)	**High**	Opioid therapy increases 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) 9 Critical	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000	**526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
Pain 9 Critical	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm	cm Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Opioid therapy slightly improves pain
Physical function	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from:		Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy slightly improves physical function

9 Critical	12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months			
Addiction 9 Critical	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Opioid therapy increases the risk of addiction.
Fatal overdose 9 Critical	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy increases the risk of fatal overdose.
Non-fatal overdose 9 Critical	Based on data from 9,940 patients in 1 studies	Risk of non-fatal overdose is 0.2%.	**Moderate** Due to serious imprecision	Opioid therapy increases the risk of non-fatal overdose.
Diversion 9 Critical	Based on data from 472,200 patients in 1 studies	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	Opioid therapy probably increases the risk of diversion.

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Pain (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;
Physical function (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;

Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** The study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State. ; **Imprecision: Serious** Small number of events and no confidence interval provided. ; **Publication bias: No serious**
Diversion	**Intervention reference:** Primary study	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Recommendation #3

Patients with an active substance use disorder and chronic non-cancer pain

Strong Recommendation | AGAINST

We recommend against the use of opioids

Clinicians should, if not yet addressed, facilitate treatment of the underlying substance use disorders

Rationale

Low quality evidence suggests a possible substantial increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with active substance abuse disorder using opioids.

Clinical Question/ PICO

Population: PICO 3: Patients with chronic non-cancer pain with an active substance use disorder whose non-opioid therapy has been optimized

Intervention: Trial of opioids

Comparator: Continue established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with an active substance use disorder compared to patients without an active substance use disorder.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids	Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 5 Important	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Opioid therapy increases gastrointestinal side effects in patients with active substance use disorder.
Pain (difference in patients who achieve the MID or greater) 5 Important	Relative risk 1.29 (CI 95% 1.24 - 1.34) Based on data from 13,948 patients in 35 studies. (Randomized controlled) Follow up 12-24 weels	**424** per 1000	**547** per 1000 Difference: **123 more** per 1000 (CI 95% 102 more - 144 more)	**High**	Opioid therapy increases 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) 5 Important	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000 **526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
Pain 5 Important	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm (Mean) cm (Mean) Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Opioid therapy improves pain slightly in patients with an active substance use disorder.
Physical function 5 Important	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	(Mean) (Mean) Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy slightly improves physical function in patients with an active substance use disorder.
Addiction 5 Important	Based on data from 171 patients in 1 studies	Risk of addiction in patients with active substance use disorder is 8.9% (95% CI 3.7%-20%).	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of addiction in patients with an active substance use disorder.
Fatal overdose 9 Critical	Based on data from 18,122 patients in 3 studies	Risk of fatal overdose in patients with active substance use disorder is 0.46% (95%CI 0.19%-1.1%).	**Low** Due to very serious indirectness	Opioid therapy increases the risk of fatal overdose in patients with active substance use disorder.
Non-fatal overdose 9 Critical	Based on data from 18,122 patients in 3 studies	Risk of non-fatal overdose in patients with active substance use disorder is 0.91% (95% CI 0.39%-2.1%).	**Low** Due to very serious indirectness	Opioid therapy increases the risk of non-fatal overdose in patients with an active substance use disorder.

Details about studies used and certainty down- and upgrading		
Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious**

	reference used for intervention	**Imprecision: No serious** **Publication bias: No serious**
Pain (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;
Physical function (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious**
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious**
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse., ; **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**

Recommendation #4

Patients with a current serious psychiatric disorder whose non-opioid therapy has been optimized, and who still experience persistent problematic pain (REC #4)

Weak Recommendation

We suggest stabilization of the psychiatric disorder before considering a trial of opioids

Rationale

Low quality evidence suggests a possible large increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with serious psychiatric disorder using opioids.

Clinical Question/ PICO

Population: PICO 4: Patients with chronic non-cancer pain with a current serious psychiatric disorder whose non-opioid therapy has been optimized, and who still experience persistent problematic pain

Intervention: Trial of opioids

Comparator: Continue established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with a current serious psychiatric disorder compared to patients without a current serious psychiatric disorder.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids	Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 5 Important	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Opioid therapy increases gastrointestinal side effects in patients with current serious psychiatric disorders.
Pain (difference in patients who achieve the MID or greater) 5 Important	Relative risk 1.29 (CI 95% 1.24 - 1.34) Based on data from 13,948 patients in 35 studies. (Randomized controlled) Follow up 12-24 weeks	**424** per 1000	**547** per 1000 Difference: **123 more** per 1000 (CI 95% 102 more - 144 more)	**High**	Opioid therapy increases 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) 5 Important	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000 **526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
Pain 5 Important	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm (Mean) cm (Mean) Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Opioid therapy slightly improves pain in patients with current serious psychiatric disorders.
Physical function 5 Important	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	(Mean) (Mean) Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy slightly improves physical function in patients with current serious psychiatric disorders.
Addiction 5 Important	Based on data from 35,969 patients in 9 studies	The risk of addiction in patients with a current serious psychiatric disorder is 8.0% (95% CI 6.7%-9.5%)	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of addiction in patients with current serious psychiatric disorders.
Fatal overdose 9 Critical	Based on data from 35,969 patients in 9 studies	The risk of fatal overdose in patients with a current serious psychiatric disorder is 0.15% (95%CI 0.12%-0.18%)	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of fatal overdose in patients with current serious psychiatric disorders.
Non-fatal overdose 9 Critical	Based on data from 35,969 patients in 9 studies	The risk of non-fatal overdose in patients with a current serious psychiatric disorder is 0.3% (95%CI 0.25%-0.36%)	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of non-fatal overdose in patients with current serious psychiatric disorders.

Details about studies used and certainty down- and upgrading		
Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator**	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious**

	reference: Control arm of reference used for intervention	**Imprecision: No serious** **Publication bias: No serious**
Pain (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;
Physical function (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ;

		Imprecision: No serious **Publication bias: No serious**

Recommendation #5

Patients with a history of substance use disorder, whose non-opioid therapy has been optimized, and who still experience persistent problematic pain

Weak Recommendation

We suggest continuing non-opioid therapy rather than a trial of opioids

Rationale

Low quality evidence suggests a possible appreciable increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with using opioids.

Clinical Question/ PICO

Population: PICO 5: Patients with chronic non-cancer pain with a history of substance use disorder, whose non-opioid therapy has been optimized, who still experience persistent problematic pain

Intervention: Trial of opioids

Comparator: Continuing established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with a history of substance use disorder compared to patients without a history of substance use disorder.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuing established therapy without opioids	 Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 5 Important	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Opioid therapy increases gastrointestinal side effects in patients with a history of substance use disorder.

Pain (difference in patients who achieve the MID or greater) 5 Important	Relative risk 1.29 (CI 95% 1.24 - 1.34) Based on data from 13,948 patients in 35 studies. (Randomized controlled) Follow up 12-24 weeks	**424** per 1000 **547** per 1000 Difference: **123 more** per 1000 (CI 95% 102 more - 144 more)	**High**	Opioid therapy increases 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) 5 Important	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000 **526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
Pain 5 Important	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm (Mean) cm (Mean) Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Opioid therapy slightly improves pain in patients with a history of substance use disorder.
Physical function 5 Important	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	(Mean) (Mean) Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy slightly improves physical function in patients with a history of substance use disorder.
Fatal overdose 9 Critical	Based on data from 620 patients in 3 studies	Risk of fatal overdose in patients with a history of substance use disorder is 0.38% (95% CI 0.24%-0.62%)	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of fatal overdose in patients with a history of substance use disorder.
Non-fatal overdose 9 Critical	Based on data from 620 patients in 3 studies	Risk of fatal overdose in patients with a history of substance use disorder is 0.762% (95% CI 0.47%-1.23%)	**Low** Due to very serious indirectness	Opioid therapy may increase the risk of non-fatal overdose in patients with a history of substance use disorder.
Details about studies used and certainty down- and upgrading				

Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Pain (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;
Physical function (difference in patients who achieve the MID or greater)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse. ; **Imprecision: No serious** **Publication bias: No serious**

Recommendation #6

Patients with chronic non-cancer pain beginning long term opioid therapy

Weak Recommendation

We suggest restricting the prescribed dose to under 50mg morphine equivalents daily ,rather than a dose of 50 to below 90 mg

The weak recommendation to restrict the prescribed dose to under 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose over 50mg to potentially achieve improved pain control

Rationale

Observational study results provide moderate quality evidence of a progressive increase in the likelihood of unintentional non-fatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are very rare in those prescribed less than 50 morphine equivalents daily, but increase in those prescribed doses of 50 to 90, and though still rare, are very concerning in those prescribed doses of over 90

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain beginning long-term opioid therapy
Intervention: Limit opioid dose to a particular maximum dose
Comparator: No maximum opioid dose

Summary

A clear dose-response relationship was demonstrated for the outcomes of fatal and non-fatal overdose.
A meta-regression was performed for pain, physical function, and gastrointestinal side effects that demonstrated no dose-response relationship with opioid dose and any of these three outcomes.
No evidence was found for a dose-response relationship between opioid dose and the outcomes of addiction and diversion. The studies that informed these two outcomes included patients on a variety of opioid doses. We therefore assume that the risks presented are applicable to all doses of opioids.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No maximum opioid dose	**Absolute effect estimates** Limit opioid dose to a particular maximum dose	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 5 Important	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on gastrointestinal side effects

Pain 5 Important	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm (n/a) cm (n/a) Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on pain
Physical function 5 Important	Measured by: SF-36 physical component summary score Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	(n/a) (n/a) Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on physical function
Fatal overdose 9 Critical	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Limiting opioid dose to a particular maximum dose decreases the risk of fatal overdose
Non-fatal overdose 9 Critical	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Limiting opioid dose to a particular maximum dose decreases the risk of non-fatal overdose
Addiction 5 Important	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Limiting opioid dose to a particular maximum dose may have little or no difference on addiction
Diversion 5 Important	Based on data from 472,200 patients in 1 studies	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	Limiting opioid dose to a particular maximum dose may have little or no difference on diversion

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;

Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of events. ; **Publication bias: No serious**
Addiction	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Diversion	**Intervention reference:** Primary study	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Recommendation #7

Strong Recommendation

We recommend restricting the prescribed dose to under 90mg morphine equivalents daily rather than no upper, or a higher limit on dosing

Some patients may gain important benefit over 90mg morphine equivalents, but not on lower doses. Referral to a colleague for a second opinion regarding the possibility of increasing above 90mg morphine equivalents daily may therefore be warranted in some individuals

Rationale

Observational study results provide moderate quality evidence of a progressive increase in the likelihood of unintentional non-fatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are very rare in those prescribed less than 50 morphine equivalents daily, but increase in those prescribed doses of 50 to 90, and though still rare, are very concerning in those prescribed doses of over 90

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain beginning long-term opioid therapy

Intervention: Limit opioid dose to a particular maximum dose

Comparator: No maximum opioid dose

Summary

A clear dose-response relationship was demonstrated for the outcomes of fatal and non-fatal overdose.
A meta-regression was performed for pain, physical function, and gastrointestinal side effects that demonstrated no dose-response relationship with opioid dose and any of these three outcomes.
No evidence was found for a dose-response relationship between opioid dose and the outcomes of addiction and diversion. The studies that informed these two outcomes included patients on a variety of opioid doses. We therefore assume that the risks presented are applicable to all doses of opioids.
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No maximum opioid dose	Limit opioid dose to a particular maximum dose	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 5 Important	Relative risk 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**91** per 1000 Difference: **63 more** per 1000 (CI 95% 47 more - 81 more)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on gastrointestinal side effects
Pain 5 Important	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,948 patients in 35 studies. (Randomized controlled) Follow up 3-6 months	cm (n/a)	cm (n/a) Difference: **MD 0.71 fewer** (CI 95% 0.84 fewer - 0.58 fewer)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on pain
Physical function 5 Important	Measured by: SF-36 physical component summary score Scale: 0-100 High better Based on data from:	(n/a)	(n/a) Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Limiting opioid dose to a particular maximum dose may have little or no difference on physical function

	12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months			
Fatal overdose 9 Critical	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Limiting opioid dose to a particular maximum dose decreases the risk of fatal overdose
Non-fatal overdose 9 Critical	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Limiting opioid dose to a particular maximum dose decreases the risk of non-fatal overdose
Addiction 5 Important	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Limiting opioid dose to a particular maximum dose may have little or no difference on addiction
Diversion 5 Important	Based on data from 472,200 patients in 1 studies	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	Limiting opioid dose to a particular maximum dose may have little or no difference on diversion

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Pain	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;
Physical function	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;

Fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of events. ; **Publication bias: No serious**
Addiction	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Diversion	**Intervention reference:** Primary study	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

2 - Rotation and Tapering of Opioids, for Patients with Chronic Non-Cancer Pain

Recommendation #8

For patients currently using 90 mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Rationale

Low quality evidence suggests that substitution of an alternative opioid can reduce pain and adverse effects in patients with chronic non-cancer pain using opioids.

Clinical Question/ PICO

Population: PICO 8: Patients with chronic non-cancer pain with persistent problematic pain and/or problematic side effects
Intervention: Rotation to other opioids
Comparator: No change in opioid therapy

Summary

Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No change in opioid therapy	Rotation to other opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 9 Critical	Based on data from 524 patients in 5 studies	Mean change score on 11 point numeric rating scale was -3.3 (95% CI -3.5 to -3.1)		**Low**	Rotation to other opioids may improve pain
Physical function 9 Critical	Based on data from 206 patients in 2 studies	Mean change score of SF-36 physical function subscale was 16.7 (95% CI 15.0-18.4)		**Low**	Rotation to other opioids may improve physical function

Success of opioid rotation 9 Critical	Based on data from 349 patients in 4 studies	Across 4 studies, 253 out of 349 patients (72.5%) successfully rotated opioids.	**Moderate** Due to serious indirectness	Success of opioid rotation is probably high in this patient population.
Addiction 5 Important	Based on data from 167 patients in 2 studies	Choquette (2008) reported no spontaneous reports of abuse or addiction. Quang-Cantagrel (2000) reported one case of addiction.	**Moderate** Due to serious indirectness	Rotation to other opioids probably has little or no difference on risk of addiction.
Diversion 5 Important	Based on data from 48 patients in 1 studies	Four patients (8.3%) failed treatment due to drug diversion.	**Moderate** Due to serious imprecision	Rotation to other opioids probably has little or no difference on risk of diversion
Gastrointestinal side effects 5 Important	Based on data from 610 patients in 6 studies	Risk of nausea was 21% (95% CI 9.0-33.1%) and risk of constipation was 17.6% (95%CI 12.6-22.5%).	**Very Low** Due to serious risk of bias	We are uncertain whether rotation to other opioids improves or worsen gastrointestinal side effects.

Details about studies used and certainty down- and upgrading		
Pain	**Intervention reference:** Systematic review	**Risk of bias: No serious** Included studies lacked a comparison group. Galvez (2013) had 25% loss to follow up for efficacy outcomes, and Choquette (2008) had 24% loss to follow up for efficacy outcomes. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention reference:** Systematic review	**Risk of bias: No serious** Included studies lacked a comparison group. Galvez (2013) had 25% loss to follow up for efficacy outcomes, and Choquette (2008) had 24% loss to follow up for efficacy outcomes. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Success of opioid rotation	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Success of rotation was not measured in the same way in each study: two studies (Malinoff and Rhodin) defined as “not discontinuing therapy” (ie, lack of efficacy or intolerable adverse events); Choquette and Galvez included patients enrolled in a trial, and counted success as “not discontinuing the trial” which included lack of efficacy and adverse events, but also “noncompliance” and “withdrawn consent”. ; **Imprecision: No serious** **Publication bias: No serious**

Addiction	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Choquette (2008) relied on patients to "spontaneously" report addiction, and only followed patients for 2 months. ; **Imprecision: No serious** **Publication bias: No serious**
Diversion	**Intervention reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Low number of patients ;
Gastrointestinal side effects	**Intervention reference:** Systematic review	**Risk of bias: Serious** Included studies lacked a comparison group. ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Recommendation #9

For patients currently using 90 mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects

Weak Recommendation

We suggest tapering opioids to the lowest possible dose, including discontinuation, rather than no change in opioid therapy

Some patients are likely to experience significant increase in pain or decrease in function that persist more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Rationale

Reduction in opioid dose may reduce adverse effects including cognitive impairment and the likelihood of non-fatal or fatal unintentional overdose. Reduction, particularly if not done very slowly, may cause increased pain, decreased function, or highly aversive symptoms of opioid withdrawal.

Clinical Question/ PICO

Population: PICO 9: Patients with chronic non-cancer pain on opioids with persistent problematic pain
Intervention: Tapering of opioid
Comparator: Keeping the dose of opioid the same

Summary

Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Keeping the dose of opioid the same	Tapering of opioid	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 5 Important	Based on data from 73 patients in 2 studies	Baron 2006 (n=23): Pain was reduced from mean (SD) of 8.00 (0.30) at baseline to 3.35 (0.33) at 6 months. Harden 2015 (n=50): 40% of patients reported less pain, 28% reported no change, and 33% reported more pain after tapering.		**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether tapering of opioid improves or worsen pain
Success of tapering and end dose 9 Critical	Based on data from 73 patients in 2 studies	Baron 2006 (n=23): 100% of patients successfully tapered opioids. Harden 2015 (n=50): 47 out of 50 (94%) of patients successfully tapered opioids.		**Low** Due to serious indirectness, Due to serious imprecision	Success of tapering may be high in this patient population.

Details about studies used and certainty down- and upgrading		
Pain	**Intervention reference:** Primary study	**Risk of bias: Serious** Two out of three studies (Baron, Harden) implemented tapering strategy without a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients. ;
Success of tapering and end dose	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** These two studies defined "success of tapering" differently. Baron 2006 enrolled patients into a voluntary inpatient "detoxification" program intended to taper off of prescription opioids if the patient or physician felt that the patient was not getting benefit from high doses of opioids. No patient was referred for diversion, overuse, abuse, or addiction to opioids. The goal of the program was to taper patients completely off opioids. Harden 2015 included patients drawn from a list of patients initiated on an opioid taper at a VA medical centre. A taper was considered successful if the patient's dose at 12 months was less than the baseline dose. ; **Imprecision: Serious** Small number of patients. ;

Recommendation #10

Patients using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary opioids reduction program

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration including several health professionals (possibilities include, but are not limited to, a primary care physician, a pharmacist, a physical therapist, a kinesiologist, a psychiatrist, and a psychologist).

Rationale

Studies provide moderate quality evidence that, in patients desiring a reduction or discontinuation of opioid therapy but experiencing serious challenges in tapering or discontinuing therapy, multi-disciplinary programs can substantially increase the likelihood of successful reduction or discontinuation.

Clinical Question/ PICO

Population: PICO 10: Patients who want to taper opioids who are above the threshold dose
Intervention: Multidisciplinary Program
Comparator: No Multidisciplinary Program

Summary

In the Krumova study, 24 out of 102 patients did not completely taper but reduced dose from a mean(SD) 366.5 (524) MED to 72.6 (53.2) MED. 6 patients returned to higher doses of opioids within 12-24 months.
In the Hooten study, 2 out of 101 patients did not completely taper. One patient reduced dose from 422 MED to 22 MED; the second patient reduced dose from 365 MED to 24 MED. Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points. Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No Multidisciplinary Program	Multidisciplinary Program	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 5 Important	Based on data from 102 patients in 1 studies	Pain was reduced from 7.1 (1.8) at baseline to 5.9 (2.3) at follow up.		**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether multidisciplinary programs improve or worsen pain.
Success of tapering 9 Critical	Based on data from 203 patients in 2 studies	Krumova 2013: 78 out of 102 (76.5%) successfully tapered odd opioids in a mean of 22 days. 31 reinitiated opioid treatment within 12-24 months. Hooten 2010: 99 out of 101 (98%) patients successfully tapered off opioids.		**Moderate** Due to serious imprecision	Success of tapering is probably high with multidisciplinary programs.

Physical Function 5 Important	Based on data from 102 patients in 1 studies	Physical function improved from 26.1 (7.7) at baseline to 27.8 (9.8) at follow up.	**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain whether multidisciplinary programs improve or worsen physical function
Details about studies used and certainty down- and upgrading				
Pain	**Intervention reference:** Primary study	**Risk of bias: Serious** Studies lacked a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients. ;		
Success of tapering	**Intervention reference:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients. ;		
Physical Function	**Intervention reference:** Systematic review	**Risk of bias: Serious** Studies lacked a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients. ;		

References

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