

Rec #	Feedback Summary
1	<ul style="list-style-type: none"> ● When considering first-line therapy for patients with chronic non-cancer pain, we recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids (Strong recommendation). <ul style="list-style-type: none"> ○ Agree rate: 91% ● Hard for 'lay-patients' to understand wording of recommendations ● "Optimized" is vague, and clinician's have different interpretations on what 'optimized' entails ● Patients expressing anger at excluding cancer patients <ul style="list-style-type: none"> ○ Think that their pain experience is just as 'valid' and 'real' ● Concerns about diversity of panel members/ experts, especially lack of Aboriginal perspective (since this is an issue that affects this population greatly) ● The term "First-line therapy" is ambiguous to some ● Treatment and pain related goals of therapy should be defined when considering first-line therapy ● Elderly patients may not be suitable for non-pharma methods ● Concerns around patient assessment for CNCP (failure to assess patients appropriately for indications for opioids at opioid initiation, renewal, and when increasing the dosage) ● **Desperate call for guidance on non-pharma and non-opioid therapy <ul style="list-style-type: none"> ○ Strong feelings of lack of direction about efficacy/evidence of other options, and what to do in place of opioids (EBM chart would be helpful) ○ Time duration should be specified when alternate Tx are used as 1st line (ex. 3 months, then reassess) ○ What about concomitant prescribing? ○ Concerns about using alternative medicines, when no strong evidence ○ Call for health advocacy from practitioners to lobby for these treatments ○ Need guidance on trouble-shooting when non-pharma and non-opioid therapy is not accessible ○ Marijuana use? ● **Inaccess to Non-Pharma options <ul style="list-style-type: none"> ○ Increased costs, wait-times, need more education + research + advocacy for funding ● Opioids are useful and necessary for normal functioning (particularly from patient perspective) <ul style="list-style-type: none"> ○ Frequent addiction is misleading ○ Should instead be 'case by case' ● Non-opioids can be just as damaging ● Define: "non-opioid pharmacotherapy" and "non-pharmacological therapy" and "chronic non cancer pain" ● Wording consistency: Recommendation 1 uses "addiction" and other recommendations use "substance use disorder" ● Request for plain language explanation about how a strong recommendation could be based on low quality evidence, otherwise "not believable" ● Geriatric patients (and others) have contraindications to many non-opioid agents (NSAIDs, tricyclics, gabapentin etc.) ● Fears that waiting too long to prescribe opioids would cause reduced QOL, mental health concerns ● CDC guidelines sound more directive (e.g., "Do NOT consider opioids as 1st line) ● Non pharmacotherapy should be used before non-opioid pharmacotherapy ● At what threshold were we labelling <i>frequent</i> addiction? Many disagree that 5-12% can be labelled 'frequent' (also discordant with rec. 6& 7 that describes risk of addiction as rare but concerning → think we should be consistent) ● Flawed rationale that undermines strength of recommendation, because opioids are "effective" and "improve function" compared to non-pharma and non-opioid for those that have tried all ● A nurse practitioner thinks that "optimization" should be clarified as "interprofessional team activation" (otherwise risk GPs prescribing NSAIDs and then go to opioids)

STEERING COMMITTEE REPLY:

- All language in the guideline recommendations has been carefully considered, and conforms to GRADE guidance.
- Cancer patients, particularly those in palliative care, are likely to have different values and preferences than patients with chronic noncancer pain. For this reason, the guideline does not include cancer pain in its scope.
- We recruited patients identified by our clinical experts, and by reaching out to chronic pain organizations across Canada and advertising to their members. We selected patients from regions across Canada, as well as seeking a variety of opinions regarding the use of opioids in the management of chronic pain. Because some elements of the guideline would address the decision to initiate or not initiate opioid therapy, previous use of opioids for the treatment of chronic pain was not a requirement for inclusion on the patient panel, though 15 of 16 members had or were using opioids. Our panel included patients from the West Coast, Prairies, Ontario, and East Coast, and included patients with positive and negative experiences, or opinions, toward opioid use. We also included a member who had experience with opioid addiction, and another whose family member had suffered a fatal overdose with prescription opioids to ensure these viewpoints were represented.
- Our timeline and resources precluded a full assessment of all possible non-opioid alternatives for chronic noncancer pain; however, we have synthesized the evidence for all alternatives that have been tested directly against opioids in clinical trials, added a table summarizing the results of systematic reviews that have looked at non-opioid alternatives for chronic noncancer pain, and provided links to CADTH which has compiled the best available evidence to inform decisions on non-opioid therapies for chronic non-cancer pain (www.cadth.ca/opioids and www.cadth.ca/pain).
- We have recommended treatment if the evidence shows it is beneficial, but we acknowledge there are issues with variable of insufficient access to these treatments. It is up to governments and society as a whole to address the problem of access to services.
- We considered rates of events >5% to be “frequent”. With a pooled estimate of 5.5% risk, addiction is thus considered a frequent event; however, we have provided the data for all effect estimates so that readers can gauge magnitudes for themselves.
- We have defined chronic noncancer pain as follows: “Chronic non-cancer pain comprises any painful condition that persists for three months or longer and is not associated with malignancy.”

2

- **For patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders who still experience persistent problematic pain despite optimized non-opioid therapy, we suggest a trial of opioids rather than continued non-opioid therapy. (Weak recommendation)**
 - Agree rate: 86%
- **Vagueness Concerns:**
 - ‘substance use disorder’ and ‘history’ (Does this include cigarettes? Does history mean your whole life, or ‘clean’ for x number of days? Those prescribed benzo for anxiety or insomnia?)
 - “Serious psychiatric disorder”, “problematic pain”
 - In the rationale section, not clear whether or not “relatively frequent” applies to items after constipation
 - Define the opiate/opioid in the trial (e.g. whether combination drug or pure opioid)
 - Define “important” improvement
- **Seems like we’re saying stop non-opioid therapy, but we can use opioid *in addition to* non-opioids**
- **Concerns about practicality of *optimizing* non-opioid therapy**
 - What if you can’t access alternative therapies? Does this mean we prescribe opioids? At what point can we say we’ve ‘optimized’ non-opioids?
 - Optimization will depend on demographics/location/resource availability
 - Non-drug multidisciplinary therapies are often done inadequately, so may not be truly optimized
 - How are pain and functional outcomes to be objectively and reliability measured? What tools does the CPG recommend using?

- **Concern that we are being too lenient or ‘soft’ on opioids**
 - makes opioids sound like a second-line therapy rather than last line therapy
 - Reads that opioids are the unimodal way forward, and if it doesn’t work there’s no more options
 - Gives clinicians permission to fall back on these quickly, suggest more ‘rigid’ wording to emphasize that opioids should be considered last
- **Ambiguity about what constitutes an adequate trial of opioids**
 - Guidance needed on lower risk opioids, dosing, titration schedule, patient-level material on what to expect, use + dose of contaminant non-opioid drug therapies
- Disagreement on “*modest* improvements in pain function” (over vs. underestimation)
- Concerns about stigmatizing psychiatric patients (e.g., “they’re pain is just as valid”)
- Those that agree do so because patients should decide whether or not the results are ‘worth’ the side effects
- Conduct a clinical assessment of the likely mechanism of pain to guide treatment choice rather than simply moving on to opioids if the previous therapy was unsuccessful
- Address individuals without current/past substance use disorder but score high on the Opioid Risk Tool
- Comment on which particular diagnoses are more likely to benefit from opioids and which conditions are less likely to benefit
- Need for clear definition on which pain conditions should be treated with opioid therapy
 - E.g. (a) severe pain that interferes with daily function, and (b) a biomedical pain condition for which the benefits of opioid therapy have been shown to outweigh the adverse effects, eg neuropathic pain, severe osteoarthritis.
 - Specify that there’s limited evidence for potent opioid use for some pain conditions (e.g. fibromyalgia, headaches, low back pain)
 - Opioids also ineffective in neo-neoplastic pain
- In the remark, further emphasis on rapid discontinuation rather than continued dose escalation in cases of poor response would be warranted
 - More emphasis on function as a marker of success would also be warranted
- Need to incorporate exit strategy before prescribing
- Should be improvement in pain AND function, not pain OR function
- Does this apply to all pain diagnoses?

STEERING COMMITTEE REPLY:

- We have added language clarifying studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.
- Recommendation #2 does refer to opioid add-on therapy, and we have now clarified this recommendation as follows: “We suggest adding a trial of opioids rather than continued therapy without opioids.”
- We have added table 3 which provides opioid options for initiating a trial of therapy for patients with chronic non-cancer pain, and table 4 which lists opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain.
- we have added the following guidance statements:
 - Start at the lowest available dose of the opioid
 - Prescriptions should be provided by the primary treating physician only, for no more than 28 days at a time. Intervals may be shorter when initiating therapy, in cases of suspected diversion or during dose escalation
 - During dosage titration, advise patients to avoid driving a motor vehicle until a stable dosage is established and it is certain the opioid does not cause sedation. This is especially true when taking opioids with alcohol, benzodiazepines, or other sedating drugs
 - A reasonable trial of therapy should be accomplished within 3-6 months; opioids provide less pain relief after 3-months and some patients may continue use to address inter-dose withdrawal symptoms

	<ul style="list-style-type: none"> - Patients will develop tolerance and a withdrawal syndrome within as little as two to four weeks. This will significantly hamper any effort to taper opioids if the trial fails. - Other potential adverse effects of opioids that warrant consideration include falls, fractures, physical dependence, motor vehicle accidents, sleep-disordered breathing (including sleep apnea), depression and a worsening of pain itself (opioid-induced hyperalgesia) - Our subgroup analyses found no systematic different in opioid effect based on type of clinical condition. - Our systematic review found no evidence that any screening tool for risk factors has been validated.
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3	<ul style="list-style-type: none"> ● For patients with chronic non-cancer pain with an active substance use disorder we recommend against the use of opioids (Strong recommendation) <ul style="list-style-type: none"> ○ Agree rate: 86% ● REDUNDANT WORDING: "Patients with chronic non-cancer pain with an active substance use disorder and chronic non-cancer pain" ● Guidance on how to treat pain in patients with a SUD <ul style="list-style-type: none"> ○ Guidance/strategies requested for methadone, suboxone and buprenorphine ○ Guidance needed on how and where to refer suffering patients ○ ****Not reflective or realistic of practice → If pain goes untreated in these populations, this might fuel illicit drug use (patients often threaten this) ● Unethical and stigmatizing to deny SUD patients with effective pain treatment <ul style="list-style-type: none"> ○ Beliefs that a SUD should affect level of monitoring, and not whether patients get relief ● Vague: "active substance use disorder" Are alcohol and marijuana use included? Given the social license afforded to these substances, patients often deny having a SUD and will insist on opioids. <ul style="list-style-type: none"> ○ What about those on clonazepam or lorazepam taking 3 doses/day? ● There is poor access to effective addiction therapy ● Should focus on addressing pain relief and addiction simultaneously (or pain Rx should take precedence) ● Some think that using an opioid risk assessment tool should be made necessary <ul style="list-style-type: none"> ○ Non-front line specialists have a hard time assessing signs of SUD (lack of long-term PT knowledge) ● Need guidance on what treatment is available for patients on opioids who either: <ul style="list-style-type: none"> ○ a) Had an undiagnosed substance abuse problem or ○ b) Developed an SUD during opioid treatment ● Possible alternatives for treatment: multimodal treatments, addictions counselling, naloxone, community treatment programs, mandating concomitant management with a SUD professional, rapid taper, psychiatrist referral, limited quantities of titrated dose, UDT etc. ● Patients w/ addiction should be further stratified to determine contraindication "craving, continued use despite harm, compulsive use, loss of control" vs. pharmacologically dependent and/or fearful of not experiencing pain relief <ul style="list-style-type: none"> ○ Further define "substance abuse" (e.g. marijuana?) Treating pain should take precedence over treating addiction ● Need more detail on how to manage patients on LTOT ● The recommendation does not differentiate mild/mod/severe SUD or nociceptive/neuropathic or constant/intermittent pain. <p>STEERING COMMITTEE REPLY:</p> <ul style="list-style-type: none"> - Agree that wording was redundant. Our 3rd recommendation now reads: "For patients with chronic noncancer pain with an active substance use disorder". - The scope of our guideline does not include management of opioid use disorder - Our systematic reviews found that chronic pain patients with an active substance use disorder are at much higher risk of developing an opioid use disorder or addiction when prescribed opioids. Given the modest average benefits of opioids (which we extrapolated, given that published trials have excluded
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patients with substance use disorder), we felt that a strong recommendation against use of opioids was warranted. Although we have made a **STRONG** recommendation to avoid opioids for chronic pain patients with an active substance use disorder, our definition of a strong recommendation does acknowledge that some patients may elect to not follow the recommendation.

- We have now detailed how studies exploring risk factors defined substance use disorder: “ The studies that identified substance abuse disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.”
- We have added guidance on practical management with LTOT (see replies to 2nd recommendation)
- Our subgroup analyses found no systematic different in opioid effect based on type of clinical condition.

4

- **For 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, we suggest stabilization of the psychiatric disorder before considering a trial of opioids (Weak recommendation)**
 - **Agree rate: 79%**
- **Vagueness Concerns:**
 - Need more clarification on what constitutes a “serious psychiatric disorder” (e.g. OCD is lower risk than personality disorder) and what “stabilization” entails (as mental disorders fluctuate through life)
 - Who and how is the stability of the psychiatric disorder being determined and documented (e.g., letter of stability from mental health professional on file prior to considering trial)?
- **Often not practical to treat mental condition first, as pain exacerbates psychiatric condition → need guidance on concurrent management**
- Concerns about being **unethical** in not providing adequate pain relief to vulnerable population (taking away patient autonomy to potentially competent patients, stigmatizing etc.)
- Need guidance on how to manage the pain of this population, especially when there’s a lack of access to adequate psychiatric care
- Is there a possibility of having a recommendation on the absolute contraindication of co-prescribing of a benzodiazepine + opioid?
- Possible ideas for **alternative treatments:** blister packing, pill counts, limited quantities, monitored medication taking, having another person administer/control medication, referral to psychiatrist, mandate co-management with a SUD health professional, short-interval prescribing, increased psychiatrist access, social work support + mental health counselling, low dose, stricter titration, UDS, online monitoring of controlled substance prescriptions, family involvement
- Would be helpful to see risk stratified by condition (schizophrenia vs. depression)
- Doctors don’t have the tools to treat poverty and psychiatric disease, especially in Aboriginal populations
- Some patients psychiatric disorder never stabilize
- Suggest that the word ‘serious’ be removed (can be subject to interpretation and doctors skirting the issue claiming their patient did not have a “serious” disorder)
- Perhaps a reference to active suicidal ideation as a reason to hold off on a trial of opioids
- There should be a consensus among psychiatrist + prescriber before prescribing opioids

STEERING COMMITTEE REPLY:

- We have now described the way in which predictive studies used to generate the evidence for this recommendation defined mental illness: “The mental illnesses identified in studies as risk factors for adverse outcomes were most typically anxiety and depression, including ICD-9 definitions, as well as “psychiatric diagnosis”, “mood disorder” and post-traumatic stress disorder.”
- We have removed the qualifier “serious”
- Our 4th Recommendation is **WEAK**, meaning that a substantial minority of informed patients are likely to make different choices. Weak recommendations mean the best choice will vary, depending on each patient’s values and preferences.

- The guideline panel restricted its formal recommendations to areas in which we had sufficient evidence to support guidance. Regarding co-prescribing of benzodiazepines with opioids, our systematic review identified 5 studies that explored the association with adverse events; however, the evidence was mixed – 3 found a significant association with harms and 2 did not. As such, we convened a group of clinical experts to draft a clinical guidance statement regarding co-prescribing with opioids which concludes: “The pharmacology suggests that sedatives and opioids would enhance the depressant effect of the other, worsening the balance of harms vs. benefits and increasing the risk of cognitive effects, falls, motor vehicle accidents and drug-related death, though the supporting evidence is unavailable. The expert perspective is that opioids and benzodiazepines should very rarely be prescribed together.”
- The studies identified by our systematic review did not stratify risk based on specific mental illness.

5

- **For patients with chronic non-cancer pain with a history of substance use disorder, whose non-opioid therapy has been optimized, and who still experience persistent problematic pain, we suggest continuing non-opioid therapy rather than a trial of opioids (Weak recommendation).**
 - **Agree rate: 69%**
- What does history of substance abuse mean specifically? Does it include smoking cigarettes, drinking alcohol, and cannabis use? Will people reading this guideline decide to stop opioids on patients with past histories of SUD who have been stable for years?
 - Additional concern is that denying patients on the basis of OUD is stigmatizing, especially for those who have been stable for many years
 - Consider that substance use disorder can result from inadequately managed pain
 - There is a danger that patients will relapse and seek out illicit drugs
 - Suboxone or structured opiate therapy should be considered
- Why not try a trial of low dose of (abuse deterrent, long-acting) opioids with increased vigilance and monitoring? If at any time the OUD is thought to be present, discontinuation should occur
 - Use opioid contracts, UDS, daily dispensing
 - Refer to a specialist
- Why persist with non-opioids if they’re not working?
 - Danger of gastric and liver problems resulting from the use of Tylenol and anti-inflammatories
 - Another concern of non-opioid therapies is that they’re not always free and/or accessible
 - Moreover, continuing therapies that already have not demonstrated efficacy will result in very poor compliance and unfair labelling of patients as such
- If these doses are strictly applied:
 - even starting doses of methadone and suboxone would exceed these thresholds; moreover, conditions such as neuropathic pain and CRPS are difficult to treat and typically require higher doses
 - As people with OUD have lower pain thresholds, this will under-treat their pain
- Contradicts the statement that pain control is the “most important consideration” in Values Statement
 - Emphasize the importance of function as the priority in assessing how well a patient is doing on therapy
- Miscellaneous:
 - Why not set the dose at 60mg, as morphine typically comes in 30mg?
 - In the actual guideline, 6 and 7 are separate and 7 is missing the stem “Patients with CNCP beginning long term opioid therapy”; units are missing in rationale
- Clarify the timescale of substance use disorder (i.e. how recent?)
- Any evidence for risk in cases of remote vs recent history of substance use disorder?
- Statement on use of opioids in elderly/youth
- Need guidance on how to discuss and manage active/past substance use disorder with PTs
- Wording suggestion: "suggest continuing non-opioid therapies and a trial of opioids which is closely monitored"
- Patients will be motivated to lie

STEERING COMMITTEE REPLY:

	<ul style="list-style-type: none"> - We have now detailed how studies exploring risk factors defined substance use disorder: “ The studies that identified substance abuse disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.” - Our 5th Recommendation is WEAK, meaning that a substantial minority of informed patients are likely to make different choices. Weak recommendations mean the best choice will vary, depending on each patient’s values and preferences. Moreover, the weak recommendation indicates that clinicians should acknowledge that different choices will be appropriate for individual patients, and help each patient arrive at a management decision consistent with his or her values and preferences. We have made this explicit in the final guideline. - Our threshold of 50mg MED/day is based on the studies identified in our systematic review. Evidence for all recommendations is presented in the final guideline.
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6/7	<ul style="list-style-type: none"> ● For patients with chronic non-cancer pain beginning long term opioid therapy, we suggest restricting the prescribed dose to under 50mg morphine equivalents daily (Weak recommendation, Moderate quality evidence). We recommend restricting the prescribed dose to under 90mg morphine equivalents daily rather than no upper, or a higher limit on dosing (Strong recommendation). <ul style="list-style-type: none"> ○ Agree rate: 72% ● What about patients who are well-controlled on doses above the suggested threshold? <ul style="list-style-type: none"> ○ Regulatory bodies are likely to interpret the suggested dose as a ceiling dose, which would deprive patients of needed medications and render them vulnerable to seeking out drugs from illicit sources ○ The increase in a potential side effect from very rare to rare is unlikely to be important to most patients ● Consider that dose requirements vary dramatically between patients due to pharmacogenomics, age, weight, etc ● If extended release opioids are used, this dose does not allow for breakthrough dosing <ul style="list-style-type: none"> ○ There should be a separate recommendation for short-acting opioids such as sublingual sufentanil ● Referral to a specialist may not be practical due to long wait times and lack of accessibility in rural areas; moreover, it is unlikely that someone previously uninvolved in the patient’s care and who does not know the patient well will recommend going above 90mg ME ● There are more effective ways to mitigate the risk of unintentional fatal overdose, such as better provider and patient education, opioid contracts, frequent functional assessments, BPI, UDS, reducing amount of meds on hand/daily dispensing ● The remark should be integrated into the actual recommendation, as no one will pay attention to the former ● There is value in a start low, go slow approach, but consider that the time it takes to titrate to an appropriate dose can be excruciating for a patient ● More information needed on: <ul style="list-style-type: none"> ○ Hyperalgesia ○ Co-analgesia ○ What constitutes clinical improvement in pain and appropriate functional measures ● Clarify “colleague” (i.e. only colleagues w/ opioid prescribing experience?) ● Statement on use of weak opioids before potent opioids? ● Statement on varying initial dose for PTs at high risk for opioid toxicity (e.g. renal, hepatic, or respiratory impairment) ● Might be helpful to add parts of the rationale to the recommendation text so prescribers are aware that dose ceiling recommendations are based upon harms and risk observations vs. evidence that higher doses are ineffective ● Explicitly state that continued escalation of dose without evidence of significant benefit should be avoided ● Why is recommendation 6 restricted to those initiating opioid therapy?
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- Emphasize that functional achievement should dictate dose
- Must mention opioid tolerance/dependence
- CDC guidelines specify IR → should also make this specification

STEERING COMMITTEE REPLY:

- Recommendations 6 & 7 apply to opioid-naïve patients, not legacy patients. We address patients already using high dose opioids in our 9th recommendation.
- Our remark to acquire a consult from a colleague prior to prescribing ≥90mg MED/day does not refer to a specialists – any colleague that prescribes opioids for chronic pain is sufficient.
- There is sparse evidence for opioid risk mitigation strategies – too little to make any formal recommendations.
- We do not have direct evidence on the topic of opioid hyperalgesia, but do acknowledge this issue with the following Practical Guidance that appears in the full guideline: “Similar to other pain medications, long term therapy with opioids has low quality evidence for ongoing benefit in pain and function and has long-term side effects. Opioid benefits may attenuate with time (owing to tolerance) and for some patients may come to be defined, in whole or in part, by the relief of interdose withdrawal symptoms. Moreover, the potential harms of opioids generally increase with dose and some may not be attributed to the drugs (particularly depression, hormonal disturbance, sleep disturbance and opioid-induced hyperalgesia).”
- We have added the following statement to the guideline regarding opioid dose: “Meta-regression of within-trial comparisons of different doses of opioids found moderate-quality evidence against a dose-response effect for pain relief ($p = 0.49$) or functional recovery ($p=0.22$); however, there is likely a dose-dependent increase in the risk of non-fatal opioid overdose: 0.2% for <20mg MED/day; 0.7% for 50-99mg MED/day; and 1.8% for ≥100mg MED/day. There is an increased risk of fatal opioid overdose with higher doses: 0.1% for <20mg MED/day; 0.14% for 20-49mg MED/day; 0.18% for 50-99mg MED/day; and 0.23% for ≥100mg MED/day.”
- We have made separate recommendations for opioid-naïve patients and legacy patients because the literature we identified makes this distinction.

8

- **For patients with chronic non-cancer pain currently using 90mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects, we suggest rotation to other opioids rather than keeping the opioid the same (Weak recommendation).**
 - **Agree rate: 83%**
- Physicians do a poor job of rotating
 - Lack of information and evidence concerning equi-analgesia and variance between equianalgesic tables
 - Issues with record-keeping (e.g. patient can go to the pharmacist and ask for the previous opioid that they were on prior to rotation because “this one isn’t working”)
- **Why not combine recommendations 8 and 9?**
 - If a patient demonstrates tolerance, that should be an indication to taper/discontinue
- Impractical because:
 - Patients may not be covered for some MEQ converters (e.g. buprenorphine, tapentadol)
 - Patients are concerned about withdrawal
- Important to identify function, neuroplasticity, and expectations in management. Important to use metrics of pain and function with a BPI, Pain Disability Index, DN4, PHQ9, GAD7, Sleep Questionnaire, Kinesiphobia, and Catastrophizing scales
- Can this recommendation be similar to how Limited Use Codes function, such that a patient currently taking > 90 mg morphine equivalents per day can't pick up their next prescription of same until they have tried an opioid rotation?
- Refer to a pain specialist
- **Phrasing concern:** severe chronic pain is always persistent and problematic, it is best to stick with the medication that has worked better for the patient over anything else rather than switching arbitrarily or to try to sneakily reduce the dose

- **Phrasing concern:** specify that this is for patients who previously got adequate pain relief on a dose of under 90mg but are now experiencing tolerance; the way it is currently phrased makes it seem as though everyone should be able to achieve adequate pain relief under that threshold (90mg)
- Need guidance on how to deal w/ aberrant behaviors during opioid rotation
- the same" → "We suggest rotating to a different opioid rather than using the same opioid"
- Providers should first try to discern why a PT "needs" more than 90 mg morphine equivalents
- Wording issues:
 - **Rephrasing** (awkward wording): "We suggest rotating to other opioids rather than keeping the opioid
 - **Inconsistent wording w/ previous recommendations:** "Morphine equivalents of opioids per day" used in rec 8 vs. the previously used "morphine equivalents daily"
- Need guidance on how to rotate opioids (i.e. how many times)

STEERING COMMITTEE REPLY:

- We have attempted to address concerns regarding accidental dose increase with rotation by including an opioid conversion table and the following guidance: "Recognizing that equianalgesic tables provide only a rough approximation of equivalent opioid potency, calculate the equianalgesic dose of the new opioid based on Table 5 and reduce the calculated dose by 25-50% to minimize the risk of inadvertent overdose."
- In the full guideline we have added practical information, including the following: "Opioid rotation may be useful in some patients with uncontrolled pain, intolerable side effects and/or the need to switch to a new route of opioid administration (e.g. transdermal). One common scenario for opioid rotation is the switch from morphine to any other conventional opioid because active morphine metabolites can result in drowsiness and confusion – especially in the setting of renal failure... For patients in whom the rationale for opioid rotation is severe uncontrolled pain, administration of the equianalgesic dose without dose reduction may be reasonable. Rotation from conventional opioids to methadone is more complicated and is best carried out by experienced practitioners. Clinicians may consider the following guidance when opioid rotation is used as a strategy to reduce dose:
 1. Decrease the total daily dose of the current oral opioid 10-30% while starting the new oral opioid at the lowest total daily dose for the formulation
 2. Decrease the total daily dose of the current opioid 10-25% per week while titrating up the total daily dose of the new opioid weekly by 10-20% with a goal of switching over 3-4 weeks

Practitioners may wish to use the Switching Opioids Tool as a guide when rotating opioids:
http://nationalpaincentre.mcmaster.ca/opioidmanager/documents/opioid_manager_switching_opioids.pdf

9

- **For patients with chronic non-cancer pain currently using 90mg morphine equivalents of opioids per day or more, we suggest tapering opioids to the lowest possible dose, including discontinuation, rather than no change in opioid therapy (Weak recommendation)**
 - **Agree rate: 80%**
- No discussion on hyper analgesia/how to measure it
 - Providers should have conversations with PTs on tolerance
 - PTs upset over the care of "drug-addicts" being prioritized over their own
- Concerns over feasibility of recommendation and difficulties explaining reduced dosage to PTs
- Need to be more specific on how to measure function
- Include commentary on utilizing the multidisciplinary team for the taper and ensuring the optimized use of non-opioid and non-pharmacological therapies
- **Suggested rewording:** "potentially abandoned" (might be subjective and non-professional) → "tapering may be paused and re-initiated after a period of time"
 - Being unclear may result in physician stating they tried and never attempt to try again w/

- patients on high dose opioids indefinitely
 - **Suggested rephrasing:** Rationale undercuts the recommendation... "If the reduction of opioids "may cause increased pain, decreased function, or highly aversive symptoms of opioid withdrawal," then why follow recommendation number 9?
 - Recommendation may appear to be conflicting: "On the one hand it says to limit the dose to 90mg ME, but that tapering can be quickly abandoned (within 1 mo) if patients have increased pain or decreased function. It seems if the clinician cannot decrease the dose to less than 90mg ME then they will be in violation of a new standard. Yet patients will insist there is "an out" that tapering can be abandoned."
- **Suggested rewording:** "suggest tapering opioids to the lowest possible EFFECTIVE dose"
- "The draft guideline itself has a more complete version of the wording: "For patients with chronic non-cancer pain currently using 90 mg morphine equivalents of opioids per day or more, with persistent problematic pain and/or problematic side-effects..." (Note the latter phrase "with persistent problematic pain and/or problematic side effects...")"
- Consider advising people to get to or under the ceiling dose by a planned medically supervised tapering regime in addition to maximization and /or concurrent use of psychological support and non-opioid pharmacological approaches
 - The statement "tapering opioids to the lowest dose" is vague and assumes that practitioner has the patient on a higher than needed dose which is implying substandard care
- Guidance on specifics of tapering (especially PTs currently on high doses of opioids) is needed
 - E.g. Recommended starting dose for opioid-naive patients
- Need for primary care physicians to have tools to assist with patient education
- Highlight "suggest" and emphasize individual considerations
- Include statement on special considerations for remote, rural communities
 - Lack of multidisciplinary programs and resources for treating addiction in rural areas
 - Even where multidisciplinary programs exist, these resources generally only se PTs w/ chronic pain for a comorbidity and do not address the pain itself
- Recommendation may need a caveat for clinicians to evaluate function, risk, and conversation with PT before tapering
- Suggestion for cognitive therapy
- "Agree with recommendation, but it should not be only for people on 90 mg MEDD. This should be the standard for every patient, regardless of dose. Constant re-evaluation of dose, effectiveness, side effects, coping, physiologic change in pain generators over time, etc ought to be a standard of care."
- Include qualifying statement indicating that this recommendation if only for patients that have non-opioid or lower opioid treatments available to them.
- Methadone programs useful in reducing dependency/need for frequent dosing
- Q: "What validated pain & function measurement tools does the CPG recommend using to guide tapering and possible discontinuation?"
- Need clearer explanations on the significance of the 50 & 90 OME daily thresholds
- **"Potentially abandoned"** gives care providers a "license to abandon tapering altogether"
 - Previous suggestion: "tapering may be paused and re-initiated after a period of time"
- PTs may experience withdrawal symptoms for up to 6 months... Abandoning after 1 month is insufficient time
- Combine recommendations 8/9
 - Recommendation 8 seems to contradict 9: "Are you saying that it is important to get the pain/side effects under control while or before initiating the taper? If so then clause 9 should come before clause 8."
- Statement on structured opioid therapy for tapering?
- How to deal with narcotics left behind in palliative cases? (Recommendation: "collection and regular disposal of meds left by palliative PTs)
- Wording issues:
 - **Wording unclear:** Does this recommendation pertain to PTs whose pain is controlled or not controlled at the particular opioid dose?
 - **Inconsistent wording w/ previous recommendations:** "Morphine equivalents of opioids per day" used in rec 8 vs. the previously used "morphine equivalents daily"

STEERING COMMITTEE REPLY:

- We have reworded the recommendation as follows: “We suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.”
- There are risks to decreasing the dose, including opioid withdrawal. Moreover, the evidence supporting benefits of reducing opioid dose - decreased risk of unintentional overdose, and improved function - comes from low quality observational studies. It is thus reasonable for one patient, informed by their physician of the benefits and risks and the associated uncertainty, to choose to try lowering their dose. Another might choose to leave well enough alone. Recognizing this as a value and preference sensitive decision, the guideline panel made a weak recommendation for reducing opioid dose.
- We have drafted the following Practical Information that now accompanies this Recommendation:

“There are a number of specific reasons to consider opioid tapering:

- Lack of improvement in pain and/or function
- Nonadherence to the treatment plan
- Signs of substance misuse
- Serious opioid-related adverse event
- Patient request

Otherwise, all patients on long-term opioids at all doses should be regularly evaluated and counselled about the benefits and harms of ongoing therapy and the potential benefits of tapering.

Similar to other pain medications, long term therapy with opioids has low quality evidence for ongoing benefit in pain and function and has long-term side effects. Opioid benefits may attenuate with time (owing to tolerance and/or hyperalgesia) and for some patients may come to be defined, in whole or in part, by the relief of interdose withdrawal symptoms. Moreover, the potential harms of opioids generally increase with dose, and some may not be attributed to the drugs (particularly depression, hormonal disturbance, sleep disturbance and opioid-induced hyperalgesia).

Patients on high doses (≥ 90 mg MED/day) should be prioritized for gradual opioid tapering. The balance of benefits and harms often becomes unfavourable particularly at doses above 90mg MED/day. For these patients the potential harms of therapy often outweigh the benefits the patient can achieve in terms of pain and function.

Patients should be actively engaged in a discussion about the merits of gradual dose reduction, including the potential for better pain control and quality of life. Prepare the patient for tapering by optimizing non-opioid strategies for pain management, setting realistic functional goals, optimizing psychosocial support, creating a schedule of dose reductions and follow-up visits and having a plan in place to manage withdrawal symptoms and emerging pain. Establishing a plan with patients takes the uncertainty out of the process and helps engage them in the process (see Appendix 1 for a Patient Information Sheet for Tapering).

A gradual dose reduction of 5-10% of the morphine equivalent dose every 2-4 weeks with frequent follow up is a reasonable rate of opioid tapering. Switching the patient from immediate release to controlled release opioids on a fixed dosing schedule may assist some patients in adhering to the withdrawal plan. Patients and physicians may wish to consult a pharmacist to assist with scheduling dose reductions.

Alternative methods of tapering include:

Reducing the dose rapidly over a few days/weeks or immediately: This method may result in severe withdrawal symptoms and is best carried out in a medically supervised withdrawal centre

Tapering with methadone or buprenorphine-naloxone preparations: patients may be rotated to

	<p>methadone or buprenorphine-naloxone and then gradually tapered. In Canada, all physicians prescribing methadone require a Federal exemption for pain or addiction. The requirement for supplementary training for the use of buprenorphine-naloxone varies from province to province. If unfamiliar, clinicians should consult with someone knowledgeable with buprenorphine-naloxone use.</p> <p>In patients struggling with the tapering plan (distressing or intolerable pain/withdrawal symptoms/decreased function which persists longer than 4 weeks), pausing the taper and re-evaluating the patient's pain/clinical status/coping mechanisms and the approach to tapering can help formulate a go-forward plan. (See Recommendation #10)</p> <p>In patients with the emergence of significant mental health symptoms and/or ambiguous drug-related behaviours, consultation with local experts is advised.</p> <p>Patients should be encouraged to taper to the lowest opioid dose achievable without a loss of previously achieved function. Some patients may not eliminate use of opioids, but any reduction in dose may be beneficial.”</p>
10	<ul style="list-style-type: none"> ● For patients with chronic non-cancer pain using opioids and experiencing serious challenges in tapering, we recommend a formal multidisciplinary program (Strong recommendation, Moderate quality evidence) <ul style="list-style-type: none"> ○ Agree rate: 90% ● Large concerns (over 50-60% of survey responders) regarding wait times, cost, feasibility, and availability of multidisciplinary teams <ul style="list-style-type: none"> ○ Should be statement on what to do when the services are unavailable ○ Concerns over the burden of a multidisciplinary program on both patients and primary care physicians in rural areas ○ “Pharmacists have often not been on board with opioid tapering. How will they become aware of these guidelines? Does their regulatory body support the implementation of these guidelines?” ○ Patients need time to build rapport with the various members of multidisciplinary teams ○ PTs expressed frustrations over conflicts within the multidisciplinary teams ○ Where are these services provided? ○ Suggestion to offer extra interdisciplinary support to primary care physicians (e.g. ECHO, telehealth, access to consultative expertise) ● Opioid use in children/teens? ● No mention of addiction expert/management services? ● Tapering should be tied to function and withdrawal syndromes ● Need to be more specific regarding when to taper (e.g. after a certain amount of time, serious side effects) ● Multidisciplinary team should be involved in all aspects/stages of opioid use and for all PTs ● No mention of nurses or chiropractors in multidisciplinary team ● Statement may imply that “PTs aren’t giving their best effort [toward tapering] and every PT is capable of successfully being tapered off opioids” ● Suggest pain self-management and pain education programs ● Consideration that challenges tapering may reveal an underlying opioid use disorder ● Use of methadone and cannabinoids for tapering ● Suggested rephrasing: qualify “serious challenges” in tapering ● Need for a provincial list of referral programs for physicians to access ● Teams should be available throughout all stages of opioid use ● Pain specialists may be more available than interdisciplinary teams ● Recommendation presumes that all PTs can/should have their opioids tapered ● Emphasize that team should support the prescriber rather than assume the care of PT ● Occupational therapists and addiction specialists should be included in team ● Need guidance on how providers can make the best use of multidisciplinary teams

- Need to name these programs and provide info on how to refer to them
- Indicate which are covered by ODB/OW/ODSP, etc.

STEERING COMMITTEE REPLY:

- We recognize the resource issue associated with this recommendation, and have made the following remark: “Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).”
- We have 2 pharmacists associated with our team, who have committed to helping with knowledge translation efforts to their colleagues.
- The scope of our guideline is limited to adults.
- We have now added nurses and chiropractors to the list of interdisciplinary team members.

Other Feedback

- Survey should include “qualifications” response or keep it anonymous
- Include statement in guidelines about any possible ties of panel members to pharmaceutical industry
- Guideline lacks practical guidance for physicians
- “Pain should not be treated by “one size dose fits all” dose
- Needs more info on prescribing, assessment of pain, risk assessment, **monitoring**, and problem management
 - No mention of opioid contract/informed consent, urine drug testing, pain/function scoring tool, or opioid risk tool?
 - No mention of prescriber access to PT’s prescription drug use history
 - Include statement on maximum quantity of opioids to be prescribed/dispensed at any one time
 - Include statement on how to prevent multi doctoring and how to identify physicians who overprescribe
- Concerns over dose reduction in progressive non-cancer diseases (E.g. Kennedy’s Disease)
- Lack of information on what pharmacological and non-pharmacological treatments have an evidence-base with clear information on duration of trials, attrition and adverse effects
- No information on self-management
- Needs info on patient/family education on Sx of overdose, safe storage, and obtaining naloxone kits
- Needs comment on starting w/ short acting or long acting formulations
 - No info on high dose formulations (e.g. fentanyl patches on opioid-naive)
- No information on transition from acute to chronic pain
 - Include acknowledgement of how people arrive at having chronic pain
- Concern over lack of pain consultants, NPs, and addiction physicians on the voting committee
- **Reword for inclusive terminology:** “Primary care providers” or “clinicians” vs. “physician”
- Need for specific references for data on long-term use (>3 months, especially > 12 months)
- Suggestion for workplace intervention specialist and workplace accommodations for individuals relying on opioids while maintaining full-time jobs
- Clarify whether recommendations are legally enforceable and whether they take precedence over the current opioid policies recommended by each province’s College of Physicians and Surgeons
- **Recommendation regarding sedating agents**
 - Recommendation regarding benzodiazepine and z-drugs?
- **Concerns over separating non-cancer vs. cancer pain**
 - Provide a refreshed definition of chronic non-cancer pain at beginning (how is “chronic” defined?)
 - Be more specific about which patients are being excluded re: “cancer pain”
 - i.e. excluding/including PTs... w/ pain from cancer tissue destruction during progressive cancer and/or its treatment or PTs w/ persist pain and cured or controlled cancer?
- Role of other factors (e.g. concomitant disability, function, mental health, poverty, and coping) in opioid use are not addressed

- **Post morphine equivalents for other common opioids**
- No mention of genetic differences and how they influence opiate response
 - Having the genetic tests for codeine will help significantly in our ability to guide patient management. "Consider pharmacogenetic testing for patients, especially those with disorders that increase chance of dependence, or altered response"
- Create a simple graphic that includes recommendations that could be reviewed by primary care providers with patients seeking opioids
- Guideline should include statement on rate of suicide for PTs with untreated or undertreated chronic pain
- Lack of representation from Western Canadian care providers, especially when opioid overdose is particularly problematic in BC
- Physicians need a system to look up all PT prescriptions and an alert system for PTs receiving multiple prescription for the same medication
- Need to include more info on long-term harms of opioids and identifying/treating opioid use disorders
- Need more info on managing patients w/ reduced QOL when tapering
- No comment on naloxone?
- Include statement on risks of opioid in elderly
- Handouts for patients would be useful
- Expand guideline to include severe illnesses that are not life-ending (palliative but not terminal)
- **French translation was poor** (stated in French)
- Survey doesn't have a "back button" to review or revise prior comments
 - Responders didn't know there would be a "general feedback" section
- Responders want a copy of their answers
- Many responders called for a need for additional provider + patient education on opioids, non-pharmacological pain treatments, and pain management
- Concern that no experienced addiction physicians on panel
- How were the members of the patient advisory committee chosen? Do they truly reflect all the breadth of experiences?
- **Regarding Values and Preferences Statement:**
 - Why not mention the importance of assessing and valuing functional goals as an alternative marker of success? (not just pain).
 - Too much of a focus on patient autonomy
- Lack of guidance on polypharmacy with other sedating drugs
- GRADE discourages strong recommendations when quality of evidence is low, but there are situations where strong recommendations may be warranted despite low quality evidence:
 - One of these is when low quality evidence suggests equivalence of two alternatives, but high quality evidence suggests greater harm of one. For recommendation 1, low quality evidence, much of it indirect, suggests equivalence of opioid therapy and a number of other interventions, and high quality evidence demonstrates greater harm.
 - Another situation is when high quality evidence suggests modest benefits and low or very low quality evidence suggests possibility of catastrophic harm. For recommendation 3, high quality evidence suggests modest benefit and low quality evidence suggests an elevated risk of serious harm.
- Function should be the measurement, rather than simply the goal of opioid treatment
 - Are there any studies showing functionality in terms of work performance, home life, etc.?
- Elevation of pain by sugar and other dietary factors should be addressed
- Need guidance on management of PTs w/ addiction
- **Inconsistent wording** throughout guideline RE: addiction vs. SUD
- Recommendation on risks of combining opioids w/ other CNS depressants (e.g. prescription/OTC drugs and alcohol)
- Nabilone?
- Complaints about the recommendations being overly "wordy"/not concise
- Addition of table of morphine equivalents would be appreciated
- Should be a greater emphasis on safe prescribing practices rather than dosages
 - Goals of opioid therapy need to be explicitly outlined and include improved pain and function

- “Strong vs. weak recommendation” distinction confusing for clinicians and audience
 - E.g. “Weak recommendation” for suggesting opioid trial may be used by anti-opioid physicians as a reason to not using opioids
- Restriction on two separate doses (50/90) seem contradictory → suggest replacing “restricting” with “watchful dose”
- Address difficult situations/scenarios during opioid prescribing
 - E.g. Legacy patients doing well functionally above 90 mg/eq morphine
 - E.g. How physicians can address difference between opioid withdrawal during taper/discontinuation vs. increased pain and decreased function when opioids were genuinely helpful
 - Distinguishing between addiction and withdrawal symptoms
- No definition of “clinically meaningful” improvements in pain and function
- Recommendations seem to be more geared for prescribers in tertiary care settings rather than primary care settings (where recommendations may not be readily implementable due to limited resources)
 - To what extent do the recommendations apply to both settings?
- Will the final guideline have a page including updates/corrections/errata?
- Guidance on pill counts?

STEERING COMMITTEE REPLY:

- Detailed conflict of Interest statements for Panel, Expert, and Steering Committee members are available publically at: <http://nationalpaincentre.mcmaster.ca/guidelines.html>
- The full guideline contains a Practical Guidance section for each recommendation.
- There was insufficient evidence for any risk mitigation strategy to allow for formal recommendations (in fact – the evidence that is available suggests that treatment agreements, urine drug screening, and tamper resistant formulations are ineffective in preventing opioid overdose). As such, we convened a group of clinical experts to draft clinical guidance statements regarding risk mitigation strategies; these appear in the full guideline.
- The scope of our guideline does not include acute or subacute pain.
- We have provided the following guidance for interpreting strong and weak recommendations:

Strong recommendations indicate that all or almost all fully informed patients would choose the recommended course of action, and indicate to clinicians that the recommendation is appropriate for all or almost all individuals. Strong recommendations represent candidates for quality of care criteria or performance indicators.

Weak recommendations indicate that the majority of informed patients would choose the suggested course of action, but an appreciable minority would not. With weak recommendations, clinicians should recognize that different choices will be appropriate for individual patients, and should assist patients to arrive at a decision consistent with their values and preferences. Weak recommendations should not be used as a basis for Standards of Practice (other than to mandate shared decision-making).

- We only present factors associated with outcome following opioid use that are supported by the evidence identified through our systematic reviews. Genetic factors, poverty, etc. were not among factors reported in the eligible literature we reviewed.
- The full guideline is available online in an interactive, multilayered format, including patient decision aids for all weak recommendations, here: <https://www.magicapp.org/public/guideline/8nyb0E>
- There was insufficient evidence to make a formal recommendation on co-prescribing of Naloxone, but we have provided the following clinical guidance statement:

Clinicians may provide naloxone to patients receiving opioids for chronic pain who are identified as at risk due to high dose, medical history, or comorbidities. However, the available very low quality evidence does not provide support for the hypothesis that co-prescribing naloxone with opioids for patients with chronic noncancer pain reduces fatal overdose, all-cause mortality, or opioid-related

hospitalization. Prescription of naloxone may be considered while rotating opioids, as patients may have difficulties understanding the concept of different potencies and take more than their prescribed dose.

There is evidence to support prescription of naloxone for patients who are addicted to opioids or recreational users, especially those using intravenous drugs, to be administered by family or friends in the case of overdose pending arrival of emergency services. Many patients at risk of opioid overdose are willing to be trained and use naloxone in the event of an emergency. Moreover, these programs are well received by staff, clients, and local agencies.

It is possible that naloxone prescription will highlight the potential for serious adverse events such as overdose and death for patients and their families, leading to increased vigilance and critical consideration of the benefit of the treatment.

- We have developed a Patient Information Sheet for Tapering available here:
<http://nationalpaincentre.mcmaster.ca/guidelines.html>
- We have re-done the French translation, and believe that the current version is of high quality.
- We considered substituting our values and preferences for those of patients, but decided against this as we felt it was important to prioritize patient autonomy.
- There is evidence for role functioning and opioid use. We are committed to publishing all systematic reviews that informed our recommendations which will include this evidence. All reviews will be referenced in the online guideline as they are published.
- We have supported the development of a CME online course, that will be provided by Memorial University, that will focus on the implementation of the guideline recommendations in practical situations.