The authors respond to "Inconsistencies in the 2017 Canadian Guideline for Opioids for Chronic Noncancer Pain"

We value Drs. Weinberg's and Baer's careful review and feedback[1] on the 2017 Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain,[2] and we would like to respond.

The guideline has undergone external peer review to evaluate the rigour that went into its development, as is the case with all guidelines published in *CMAJ*. The current review was undertaken to ensure that a financial conflict of interest declared by 1 of 15 voting panel members did not leave the guideline "tainted" by the influence of industry.[3]

In brief, the guideline's recommendations are to avoid opioids as first-line therapy for chronic noncancer pain, avoid prescribing opioids to individuals with past or present substance use disorder or other active psychiatric illness, to keep the daily dose of opioids below 90 mg (and ideally below 50 mg) morphine equivalent dose per day (MED/day) when opioids are prescribed, and to approach patients who are currently prescribed 90 mg MED/day or greater to reduce their opioid dose very gradually, if possible.

The review by the Canadian Institutes of Health Research (CIHR) has now been completed, and concluded: "the perceived [conflict of interest] COI of one individual on the voting guideline panel did not have any impact on the final recommendations. CIHR concludes that the 2017 Canadian guideline does provide unbiased, evidence-based guidance to clinicians on opioid prescribing practice that is aligned with international comparators." The guideline steering committee is confident that implementation of the guideline recommendations will improve the care of patients with chronic noncancer pain and decrease the harm caused by prescription opioids in Canada.

Table 3 in Appendix 1 (available at www.cmaj.ca/content/189/18/E659/suppl/DC1) is meant to provide ready guidance for opioid options when starting a trial of therapy for patients with chronic noncancer pain. The comments regarding codeine are present in the MAGICapp version of the guideline ("Prodrug must be converted to morphine in the liver; this occurs with great inter-individual variability"), which is available at www.magicapp.org/public/guideline/8nyb0E; however, this text does not appear in Appendix 1 of the *CMAJ* article. We thank the authors for pointing this out.

Tramadol is indeed a prodrug. Although tramadol itself interferes with monoamine reuptake, its principal metabolite (+)-M1 binds to the μ-opioid receptor with an affinity 700-fold higher than that of the parent compound. The conversion of tramadol to this metabolite is accomplished by cytochrome P450 2D6 (CYP2D6), the same process that converts codeine to morphine.[4]

Table 3 in Appendix 1 reports that oxycodone, hydromorphone and tapentadol are available in tamper-resistant formulations, which is accurate. The guideline acknowledges that there is insufficient evidence to make a formal recommendation regarding tamper-resistant formulations, and our clinical guidance statement no. 8 in Appendix 1, regarding these formulations, reads as follows: "When available and affordable, tamper-resistant formulations may be used to reduce the risks of altering the intended delivery system (i.e., from oral to nasal or intravenous injection). They do not reduce the most common mode of misuse (oral ingestion), but are less favoured by people who misuse opioids by any route. Not all payers reimburse for tamper-resistant formulations, and in some cases abuse of these formulations may lead to unique harms (e.g., particulate induced cardiac valve injury when injected). Tamper-resistant formulations are often more costly and the evidence of impact upon overall abuse of opioids, when some drugs are supplied in tamper-resistant formulations and others are not, is unclear."

This does not strike us as messaging that the pharmaceutical industry will be keen to endorse. We have included a note in Table 3, in the MAGICapp version of the guideline, highlighting that tamper-resistant formulations have not been approved by Health Canada.

Although we were unable to make a recommendation regarding immediate- versus controlled-release formulations, we hope to pursue a "living guideline" that would consider new, important information as it emerges. We are aware of a recent publication that may facilitate a recommendation regarding immediate- versus controlled-release opioid formulations,[5] and the guideline steering committee is in discussion on this issue.

The authors of the letter feel that regulators and lawyers will be confused by the use of both "good practice" and "best practice" statements. The three statements in question in Appendix 1 are, in brief, as follows: (1) Clinicians with chronic noncancer pain patients prescribed opioids should address any potential contraindications; (2) Clinicians should monitor their chronic noncancer pain patients using opioid therapy for their response to treatment, and adjust treatment accordingly, and (3) Acquire informed consent before initiating opioid use for chronic noncancer pain. We feel there is little debate regarding whether clinicians should adhere to these practices.

The terms "urine drug screening" and "urine drug testing" are often used interchangeably and do not represent an inconsistency.

The summary statements for each recommendation in Appendix 1 succinctly convey the findings of the systematic reviews, and the key information

for each recommendation provides greater detail. Accordingly, the summary statements for the sixth and seventh recommendation advise: "A clear dose–response relationship was demonstrated for the outcomes of fatal and nonfatal overdose." The key information section provides more detailed statements for each outcome, with the accompanying estimates of association. We have removed the qualifier "clear" from the summary statement (in the MAGICapp version of the guideline) to address any perceived inconsistency.

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References

1. Weinberg EL, Baer PA. Inconsistencies in the 2017 Canadian guideline for opioids for chronic noncancer pain [letter]. *CMAJ* 2017 June 26 [Epub ahead of print]. doi:10.1503/cmaj.733244.
2. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* 2017;189:E659-66.
3. Howlett K. Opioid panel chair admits conflict-of-interest lapse. *Globe and Mail* [Toronto]. 2017 May 19. Available: www.theglobeandmail.com/news/national/opioid-panel-chair-admits-conflict-of-interest-lapse/article35073017/ (accessed 2017 June 30).
4. Gillen C, Haurand M, Kobelt DJ, et al. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. *Naunyn Schmiedebergs Arch Pharmacol* 2000;362:116-21.
5. Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of opioid use and risk of opioid overdose death among Medicaid patients. *Med Care* 2017;55:661-8.

Competing interests: All authors are members of the Steering Committee for the Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain. David Juurlink was a member of the Stakeholder Review Group for the US Centers for Disease Control and Prevention guideline for prescribing opioids for chronic pain. No other competing interests were declared.