Authors' reply

In their letters, Iain McGregor and Alex Bekker state that previous systematic reviews have provided evidence of the effectiveness of cannabinoids for chronic non-cancer pain. However, three systematic reviews¹⁻³ published this year have suggested caution regarding use of cannabinoids, because of a paucity of high quality studies, and concluded that evidence for the effectiveness of cannabinoids in chronic non-cancer pain is limited by the very short duration of studies, small participant numbers, the exclusion of patients with complex comorbidities, and failure of studies to date to include common forms of chronic non-cancer pain (eq, back and neck pain, arthritis). Our observational study examined the relationship between cannabis and pain over 4 years in a large cohort of patients with pain, including those with multiple comorbidities and the most common pain conditions.⁴ We also obtained participant-level data on the potential opioid-sparing effects of cannabis, rather than relying on ecological data.

We presented comprehensive data by including not only pain intensity scores (often the only outcome measured in clinical trials), but also participants' reports of pain interference, perceptions of the effectiveness of cannabis, their reasons for using and stopping cannabis, and their opinions regarding the effect that cannabis had on their use of opioid medication. We clearly reported conflicting findings: cross-sectionally, pain levels and interference were higher among people who used cannabis than those who did not, and no association was found between cannabis use and pain and opioid dose prospectively, although participants perceived cannabis to be effective on their pain.

We acknowledged the possibility that cannabis might affect other domains that could subsequently affect perceptions of the effect of cannabis on pain. Our study has clearly stimulated debate around these potential explanations, and we hope future work will explore these possibilities.

The possibility of confounding was acknowledged, addressed, and reported in our paper. We adjusted for several confounders identified in our previous study,⁵ such as age, sex, pain duration, anxiety, history of substance use, pain severity, pain interference, oral morphine equivalent dose, and pain self-efficacy. We could not control the dose or type of cannabis that patients used, and did not obtain objective confirmation of their selfreported cannabis use. The same is true of surveys used to justify patients smoking cannabis for pain control. We discussed this in the limitations section of the paper.

Finally, regarding potential competing interests, we have previously documented deaths from opioid overdose in Australia⁶ and attributable to over-the-counter codeine,⁷ which informed decisions to make codeine a prescription-only drug in Australia. We value our independence extremely highly and retain academic independence in all its forms.

GC and LD report National Health and Medical Research Council fellowships (#1119992 and 1135991). The National Drug and Alcohol Research Centre at University of New South Wales, Australia, is supported by funding from the Australian Government, under the Substance Misuse Prevention and Service Improvements Grant Fund. Some of the authors report investigator-initiated untied educational grants from Reckitt Benckiser/ Indivior for studies of buprenorphine-naloxone (LD and MF), buprenorphine depot (LD and MF), the development of an opioid-related behaviour scale (LD), and a study of opioid substitution therapy uptake among patients with chronic noncancer pain (LD and GC). LD and MF also report an untied educational grant from Seqirus for studies of tapentadol. All are outside the submitted work. WH reports grants from Australian Therapeutic Goods Administration and personal fees as a Member of the Australian Advisory Council on Medical Uses of Cannabis, both outside the submitted work. TD declares no competing interests.

*Gabrielle Campbell, Wayne Hall, Louisa Degenhardt, Timothy Dobbins, Michael Farrell g.campbell@unsw.edu.au National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2046, Australia (GC, LD, TD, MF); Centre for Youth Substance Abuse Research, University of Queensland, Brisbane, QLD, Australia (WH); and National Addiction Centre, Kings College London, London, UK (WH)

Copyright © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

- Hauser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management—an overview of systematic reviews. *Eur J Pain* 2018; 22: 455–70.
- 2 Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018; 3: CD012182.
- 3 Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain* 2018; published online May 25. DOI:10.1097/j.pain.00000000001293.
- 4 Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health* 2018; **3:** e341–50.
- 5 Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend 2015; 147: 144–50.
- 6 Roxburgh A, Dobbins T, Degenhardt L, Peacock A. Opioid, amphetamine, and cocaineinduced deaths in Australia: August 2018. Sydney: National Drug and Alcohol Research Centre, UNSW Sydney. https://ndarc.med. unsw.edu.au/resource/opioid-amphetamineand-cocaine-induced-deaths-australiaaugust-2018. (accessed Sept 18, 2018).
- 7 Roxburgh A, Hall WD, Burns L, et al. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *Med J Aust* 2015; 203: 299.