2015

Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study

Louisa Degenhardt
University of New South Wales, ldegenhardt@epi.msu.edu

Raimondo Bruno
University of Tasmania

Nicholas Lintzeris
University of Sydney

Wayne Hall
University of Queensland

Suzanne Nielsen
University of New South Wales

See next page for additional authors

Publication Details

Degenhardt, L., Bruno, R., Lintzeris, N., Hall, W., Nielsen, S., Larance, B., Cohen, M. & Campbell, G. (2015). Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. The Lancet Psychiatry, 2 (4), 314-322.

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Abstract

Background

Classification of patients with pharmaceutical opioid use disorder and dependence varies depending on which definition is used. We compared how WHO's ICD-10 and proposed ICD-11 and the American Psychiatric Association's DSM-IV and DSM-5 classified individuals in a community-based sample of Australians with chronic non-cancer pain for which opioids have been prescribed.

Methods

We studied participants in the Pain and Opioid IN Treatment (POINT) cohort, a 2 year prospective cohort study of 1514 people prescribed pharmaceutical opioids for their chronic pain who were recruited in 2012–13 from community-based pharmacies across Australia. After giving patients the Composite International Diagnostic Interview about their opioid use, we assessed which patients would be categorised as having disorders of pharmaceutical opioid use by ICD-10, the draft ICD-11, DSM-IV, and DSM-5. We examined agreement between classification systems, and tested the unidimensionality of the syndrome with confirmatory factor analysis.

Findings

We included 1422 participants (median time of pain disorder 10 years [IQR 5–20]; median length of strong opioid prescription 4 years [IQR 1·5–10·0]; mean age 58 years). Similar proportions of individuals met lifetime criteria for dependence with DSM-IV (127; 8·9%), ICD-10 (121; 8·5%), and ICD-11 (141; 9·9%). Criteria in DSM-5 classified 127 (8·9%) participants with moderate or severe use disorder. There was excellent agreement between ICD-10, ICD-11 and DSM-IV dependence (κ>0·90). However, there was only fair to moderate agreement between ICD-10 and DSM-IV dependence diagnoses, and DSM-5 use disorder (mild, moderate, or severe). There was only good agreement between moderate to severe use disorder in DSM-5 and the other definitions. Criteria for all definitions loaded well on a single factor; the best model fit was for the definition for dependence in the draft ICD-11, the worst was in DSM-5.

Interpretation

Classification of problematic pharmaceutical opioid use varies across editions of ICD and DSM. The much lower levels of agreement between DSM-5 and other definitions than between other definitions might be attributed to DSM-5 containing an increased number of criteria and treating dependence and problematic use as a continuum. The more parsimonious ICD-11 dependence definition showed excellent model fit and excellent agreement with previous classificatory systems.

Keywords

opioids, taking, people, dependence, disorders, opioid, pharmaceutical, cohort, definitions, study, between, agreement, chronic, non-cancer, pain, (point):

Disciplines

Education | Social and Behavioral Sciences

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Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study

Louisa Degenhardt, Raimondo Bruno, Nicholas Lintzeris, Wayne Hall, Suzanne Nielsen, Briony Larance, Milton Cohen, Gabrielle Campbell

Introduction

Chronic non-cancer pain is a common cause of disability worldwide. The Global Burden of Disease (GBD) 2010 study 1 estimated that in 2010, 1·0 billion people (15% of world population) had migraines, 630 million (9%) had lower back pain, and 332 million (5%) had neck pain. Low back pain, neck pain, and migraines were the first, fourth, and eighth largest contributors, respectively, to global non-fatal health burden (years lived with disability).1 Chronic non-cancer pain can also have a major effect on social and financial well-being, and increases health costs. 2,3 The burden of chronic pain will probably increase in the future as the population ages in many high-income countries.

Despite little evidence for efficacy in use of long-term opioids to manage chronic non-cancer pain,4–6 rates of prescription have increased in many high-income countries, including the USA, Canada, and Australia. 7–11

Concern has also been rising about concomitant increases in problematic use of, and dependence upon, these opioids. 12,13 The two major classification systems for disorders of opioid use have been undergoing revision. WHO's tenth edition of ICD (ICD-10) distinguishes between harmful use (defined as a pattern of use of a psychoactive substance that is causing damage to physical or mental health) and dependence (a cluster of symptoms that typically include craving, difficulties in controlling use, persisting use despite adverse consequences, tolerance, and withdrawal). 14 In the specialty of pain medicine, dependence is often referred to as addiction,15 with less emphasis upon tolerance and withdrawal, which are considered to be physiological results of long-term opioid use and not markers of problematic use. The eleventh edition of ICD (ICD-11) is planned to be presented to the World Health Assembly in May, 2017. 16 The beta version of ICD-11 draft descriptions and clinical features of disorders were released in July, 2014. The draft proposal for substance dependence has retained the concept of a dependence syndrome, but proposes that criteria (or features) should be reduced to three (from six) and that to meet criteria for dependence, an individual needs to meet only two.

DSM-5 was released on May 18, 2013, by the American Psychiatric Association.17 The previous edition, DSM-IV, defined opioid abuse and opioid dependence18 in broadly similar ways to the terms used in ICD-10. By contrast, DSM-5 shifted to classifications of opioid use disorders (divided into mild, moderate, and severe based on number of symptoms).17 11

criteria are included; a person who fulfils at least two of these meets the definition for a use disorder. Tolerance and withdrawal are included, but a person taking opioids only under medical supervision (and not being non-adherent—eg, doctor shopping, tapering, diverting, or taking more opioids than directed) is not thought, in DSM-5, to fulfil either criteria (which we describe as conditional exclusion),17 in keeping with the view of pain physicians that under chronic administration of opioids, the development of tolerance and withdrawal is expected. The shifts in DSM-5 have not been without controversy.19–29 Questions have been raised about the validity of the new definition, the adequacy of field testing,21 the potential cultural and social biases embodied in the new approach,20 and the clinical and epidemiological effects of the lowered diagnostic thresholds.22,30,31 Other people have questioned the clinical use of the combined diagnosis of use disorders, which no longer distinguishes between episodic binge use and compulsive use.22 Some have questioned their use in cases in which doctors might be legally mandated to provide treatment if that person is not formally assessed as dependent.

Less has been written about the effect of these differing approaches to classification of people taking opioids for chronic non-cancer pain. Significant debate exists about when and how a diagnosis of opioid dependence can or should be made in persons receiving long-term opioid treatment for chronic non-cancer pain.32,33 Some investigators suggest that dependence and addiction should be considered separately in this population.26,27,34–36 Behaviours that are suggestive of dependence symptoms might arise for many reasons. For example, requests for increased doses could be due to undertreatment of pain, tolerance, or drug seeking (as a symptom of dependent use).37,38 Some investigators have questioned the relevance of these diagnostic criteria in older adults,39 in whom chronic pain is more prevalent. Absences from work or school; less frequent car or machine operation; and a general reduction in social, occupational, and recreational activities are common in patients with chronic pain. This can make it difficult to assess some of the diagnostic criteria in older adults. Additionally, approaches vary for the inclusion of tolerance and withdrawal in the diagnosis of opioid dependence in patients receiving opioids for chronic non-cancer pain.

In this study, we aim to compare how the different operational approaches to pharmaceutical opioid use disorder or dependence classify individuals in a large, national, community-based sample of people living with non-cancer chronic pain who have been prescribed opioids to manage their pain. Specifically, we aim to estimate the prevalence of pharmaceutical opioid dependence and opioid use disorder in a cohort of patients using opioids chronically with the criteria in DSM-IV, DSM-5, ICD-10, and draft ICD-11 criteria; assess criteria fulfilled by those meeting each definition of a disorder; investigate concordance between the definitions; and assess the extent to which the criteria of the varying definitions describe a unidimensional syndrome.

Methods

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Study design and setting

We studied patients enrolled in the Pain and Opioid IN Treatment (POINT) cohort. This cohort was recruited to document patterns of pharmaceutical opioid use and the risk of adverse events in a prospective cohort of patients who were prescribed opioids for chronic non- cancer pain. The POINT cohort was established in 2012. We contacted 90% of all community pharmacies in Australia (n=5332) and asked if they would assist with recruitment; 33% (n=1868) agreed to assist. The cohort includes 1514 community-based patients with chronic non-cancer pain. The methodology of this cohort has been described in detail elsewhere.40 POINT participants were aged 18 years or older; competent in English; mentally and physically able to complete the required interviews; without serious cognitive impairments as assessed by interviews (not a formal clinical assessment); and prescribed a schedule 8 strong opioid for non- cancer pain for longer than 6 weeks (eg, oxycodone, fentanyl). A history of injection drug use was not an exclusion criterion for POINT, but patients prescribed pharmaceutical opioids for opioid substitution therapy for heroin dependence or who were taking opioids for cancer pain were not eligible. The study was approved by the Human Research Ethics Committee of University of New South Wales Australia (HREC reference: HC12149).

Procedures

We assessed disorders of pharmaceutical opioid use with the Composite International Diagnostic Interview (CIDI) version 3.0.41 CIDI has been used widely in epidemiological studies in many countries,42–45 and has excellent inter-rater reliability,41 test–retest reliability,41 and agreement with clinician diagnoses.46 Phone interviews were done by trained interviewers who had received training in a computer-assisted telephone interviewing survey during

Table 1: Criteria included in classification systems and number of participants in the POINT cohort that meet criteria

the baseline interviews with cohort participants. Inter- viewers had a health or psychology degree of duration 3 years or longer, were trained in how to respond to reports of suicidal thoughts or suicidal plans, and were provided with glossaries of chronic pain drugs and disorders. We assessed patients with ICD and DSM opioid use disorder criteria.

Statistical analysis

We included all POINT members who completed the CIDI. The frequency of participants meeting each criterion for pharmaceutical opioid use disorder and dependence according to the four classification systems was reported. We examined the agreement between

numbers of participants meeting criteria for each definition of disorder. We used binary confirmatory

factor analyses to test the fit of a unifactorial model of dependence (consistent with those found for all other substances of dependence47,48) within each definition of dependence or disorder. We applied robust maximum likelihood techniques in Mplus 7.2 (Los Angeles, CA, USA). In addition, we replicated analyses with use of the mean and variance-adjusted weighted least-squares extraction procedure for estimation. We examined model-fit indices of root mean square residual (RMSEA), weighted root mean square residual (WRMR), and comparative fit index (CFI). For categorical data, values of RMSEA less than 0·06, WRMR less than 0·90, Tucker–Lewis Index (TLI) greater than 0·96, and CFI greater than 0·95 indicate good model fit.49 We compared the binary confirmatory factor values of each model, with lower values indicating a better fit.50

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

Of 1422 participants who completed CIDI assessment, 790 (56%) were women; median age 58 years (IQR 48–67).

Almost half (695; 49%) were unemployed, 499 (35%) had completed tertiary qualifications, and 760 (53%) were married or in a de-facto relationship. The full demographic, physical, and mental health characteristics of this cohort are detailed by Campbell and colleagues.51 Participants reported living with their current pain disorder for a median of 10 years (IQR 5–20). Median length of strong opioid prescription was 4·0 years (IQR 1·5–10·0). The most common opioids reported were oxycodone (862; 61%), buprenorphine (310; 22%), morphine (212; 15%), and fentanyl (211; 15%). Patients were taking a median of one schedule eight opioid (IQR 1·0–1·0).

Very similar proportions of participants met lifetime criteria for dependence (table 1) when assessed with DSM-IV (127; 8·9% [95% CI 7·5–10·5]), ICD-10 (121; 8·5% [7·2–10·1]), and ICD-11 (141; 9·9% [8·5–11·6])

classification systems (table 2). For DSM-IV and ICD-10, slightly less than one in five people met criteria for a disorder of pharmaceutical opioid use (table 2).

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Prevalence of use disorder as described in DSM-5 was considerably higher than that of opioid dependence as defined by the other three methods and was higher than use disorder as described by DSM-IV and ICD-10 (table 2). One in five (293; 20·8% [95% CI 18·8–23·0]) people in the cohort met DSM-5 criteria for pharmaceutical opioid use disorder with its standard definition in which tolerance and withdrawal do not count as symptoms of use disorder unless the person is non-adherent with their opioids (conditional exclusion). One in 20 patients (67; 4·8% [95% CI 3·8–6·0] were classified as having severe opioid use disorder with DSM-5. When tolerance and withdrawal were included as symptoms of use disorder (irrespective of the adherence), numbers increased to 414 (29% [95% CI 27·1–31·8]) overall and 88 (6·3% [5·1–7·6]) with a severe use disorder (table 2). More men than women were classified as having use disorder with ICD-10, DSM-IV, and DSM-5, and more men than women were dependent according to ICD-10, ICD-11, and DSM-IV (table 2). There were no gender differences in frequencies of people classified as having DSM-IV abuse or ICD-10 harmful use (table 2).

There were substantial differences between the definitions of disorders in the proportion of patients meeting specific criteria (table 3; appendix). In general, people meeting criteria for DSM-5 use disorder as a group had lower prevalences of each individual criterion. Those meeting ICD-11 dependence had the highest prevalences

of each individual criterion. This reflected the fact that ICD-11 had only three criteria, each of which included up to four of DSM-5 individual criteria. Compared with individuals meeting criteria for dependence with ICD-11, ICD-10 and DSM-IV, those meeting criteria for either DSM-5 use disorder (ie, with or without the conditional exclusion of tolerance and withdrawal) had much lower prevalence of the following criteria: used in larger amounts or longer than intended, great deal of time spent using and recovering from use, continued use despite recurrent social and interpersonal problems due to use, and tolerance.

The most inclusive definition of use disorder was DSM-5 including tolerance and withdrawal (appendix). An additional 121 (8%) people met criteria when there was no conditional exclusion of tolerance and withdrawal as criteria, with 14 (1%) reporting no symptoms other than tolerance and withdrawal and 107 (7%) reporting only one other symptom.

No combination of ICD-11 with any level of DSM-5 (mild, moderate, or severe) showed excellent agreement with DSM-5 use disorder (as measured with κ; appendix).52 Agreement between the DSM-5 disorder with and without the conditional exclusion of tolerance and withdrawal was good (κ=0·77; appendix). Agreement for any DSM-5 opioid use disorder (with conditional exclusions) ranged from κ=0·49 (with ICD-10) to κ=0·56 (ICD-11). Agreement was much poorer for DSM-5 when no restrictions were put on tolerance and withdrawal as criteria (κ=0·37–0·42). The highest κ values for DSM-5 classified severe use disorder were for ICD-10 (κ=0·69) and DSM-IV dependence (κ=0·67)

without imposing conditional exclusion of tolerance and withdrawal as criteria. Agreement was similar for the definition of DSM-5 severe use disorder that had conditional exclusion of tolerance and withdrawal (appendix).

When we grouped together individuals classified as having moderate or severe use disorder by DSM-5, there was still only middling agreement with ICD definitions and discrepancies in the classification of cases were more marked (appendix). A quarter (25%) and a third (34%) of those classified as dependent under ICD-10 and ICD-11 definitions, respectively, did not meet criteria for moderate or severe use disorder in DSM-5; almost three in ten of those classified as dependent under the DSM-IV definition were not classified as meeting criteria for moderate or severe DSM-5 use disorder (without conditional exclusion of tolerance and withdrawal; appendix).

The classification resulting in the greatest number of people being identified with dependence was ICD-11, followed by DSM-IV and ICD-10. Nonetheless, there was almost perfect agreement between ICD-10, ICD-11, and DSM-IV dependence, with the κ coefficient for all pairs of these classifications greater than 0·90.

Criteria for all definitions loaded well on a single factor (appendix). Generally, the items that loaded most strongly on the single factor were the psychological or behavioural symptoms of dependence or addiction, rather than the physiological ones, although all loadings were relatively high. According to model fit statistics, the best model was for the definition of dependence in the draft ICD-11, and the worst fit was for DSM-5

(appendix). The model fit was slightly better for DSM-5 with conditional exclusion (ie, the published definition) than for DSM-5 without conditional exclusion of tolerance and withdrawal.

Discussion

We assessed how different diagnostic classification systems identify disorders of pharmaceutical opioid use among people prescribed opioids for chronic non-cancer pain. Application of the criteria for DSM-5 produced much higher estimates of pharmaceutical opioid use disorders, and did not have very good agreement with both DSM-IV and with ICD-10 and ICD-11. Of the systems, the model fit statistics for DSM-5 were also the poorest, although still adequate. By contrast, dependence defined by ICD-11 had the best model fit statistics, and showed excellent agreement with the two previous classifications (DSM-IV and ICD-10).

There is considerable debate about how to identify problematic use of opioids in people who are receiving long-term opioids for medical purposes. The changes to DSM that occurred with DSM-5, which applied conditional exclusion of tolerance and withdrawal when drugs are used only as intended under medical supervision, were intended to avoid

misclassification of patients as dependent only because of normal physiological adaptations to long-term opioid use.36 We did find sizeable differences in proportions of people with opioid use disorder according to whether these conditional exclusions were in place (by contrast with previous research53). The model fit was slightly better for the definition that had conditional exclusion of tolerance and withdrawal. The effect of excluding these patients in the DSM-5 definition was most apparent in those who either were non-cases when exclusions were in place (increase of 8·6% people; table 2) and in changes of classifications from mild to moderate dependence (2·6%). This also produced better agreement with DSM-IV and ICD classifications. Given that tolerance and withdrawal will often occur on chronic administration of opioids, the architects of DSM-5 have taken the approach that these criteria are not necessarily pathognomonic for pharmaceutical opioid dependence in the context of chronic opioid therapy. Our findings provided some suggestive evidence in support of this approach in that the model fit was slightly better, and there was better agreement between DSM-5 and the other definitions with use of this definition.

However, there are other ways of making a decision that these symptoms could be considered as symptoms of a use disorder. For example, tolerance and withdrawal, if endorsed, might alternatively be counted as criteria if a patient also has non-physiological adaptation symptoms, which as we reported earlier, did load more strongly in the model. Field testing of some of these possible changes with varied groups of patients might be helpful in shedding light on some of these possibilities.

DSM-5 did not agree very well with the other classifi- cations studied. Superficially, the changes are only a minor broadening of criteria for opioid use disorders compared with other classification systems (for moderate to severe DSM-5 use disorder, there was about an extra 2% of individuals). There were, however, only poor to fair κ values between DSM-5 use disorder, and both DSM-IV and ICD-10 dependence (κ<0·6). Even when the grouping was limited to include only DSM-5 participants with

moderate or severe use disorder (with or without conditional restrictions on the inclusion of tolerance and withdrawal), there were only marginal improvements in agreement with DSM-IV dependence, ICD-10 dependence, and ICD-11 dependence.

There is little evidence for how to assess opioid use disorders in people prescribed opioids for pain (panel). Which domains are most important, and what language is the most appropriate to identify the phenomenon of addiction, is not clear. DSM-5 has taken into consideration the common physiological adaptations that occur with chronic opioid treatment (tolerance and withdrawal). Our findings provide some support for this approach, in that it resulted in a better model fit (appendix). However, we show clear differences between the approach used by DSM-5, and all other approaches to classification in this study. DSM-5 did not agree well with any of the other systems, and had the poorest model fit (appendix). It should be noted, however, that these symptoms for physiological indications of dependence typically produced the poorest fit to the dependence syndrome.

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Our work suggests that care needs to be taken in identification of this syndrome, and inquiry about these symptoms in clinical and structured interview schedules. The diagnosis of a use disorder as opposed to dependence also raises medico-legal issues. In many jurisdictions, individuals need to be diagnosed as meeting criteria for dependence to be eligible for opioid substitution therapy, or for opioid analgesic patients diagnosed as dependent to be eligible for different opioid regulatory requirements. It is not clear how this issue would be addressed within the DSM-5 classification–eg, should all people meeting criteria for a use disorder be deemed eligible? Should this eligibility be limited to individuals who meet criteria for moderate or severe DSM-5 use disorder? If all people who meet criteria for use disorder are eligible for substitution therapy, then it is clear that, at least in our cohort, this population would double. This change raises many issues; on one hand, the feasibility of provision of increased treatment coverage, the costs to patients and government, and the expansion of the number of patients with chronic pain receiving opioids for their pain who might be given an additional stigmatising label of “addicted”. On the other hand, a lower threshold would allow earlier identification of problems and allow more patients to benefit from interventions that prevent adverse events related to unintended dose escalation and poorer treatment outcomes. If only individuals with moderate or severe DSM-5 use disorder are eligible, then our study shows that many people who would be classified as dependent according to ICD or DSM-IV would not be classified as having a moderate

or severe use disorder under DSM-5.

The draft ICD-11 classification seems to have moved in the opposite direction to DSM-5. We showed that the

reduction in number of criteria classified similar proportions of patients as dependent as did ICD-10 and DSM-IV, while it also had the best model fit (appendix). The additional advantage of having fewer, simpler criteria might include better identification and more reliable diagnosis of dependence by clinicians working in a range of medical specialties.

A clear strength of our study is the scope of our recruitment: 93% of Australian community pharmacies were approached, and a third assisted with recruitment; the geographic spread of participants was also similar to the spread of the Australian population.52 However, we might not have recruited a representative sample of people prescribed opioids for their chronic pain. To investigate this possibility, during recruitment we gathered additional data from a random sample of recruiting pharmacies (71 pharmacies) on the characteristics of their customers taking opioids during the 6 week recruitment window of their involvement. Of customers recorded as purchasing opioids in these pharmacies, 52% were women (POINT cohort was 55%); and 7% aged 18–34 years, 55% aged

35–64 years, and 38% 65 years and older (vs 5%, 62%, and 33%, respectively, in POINT). Of these individuals, 63% were prescribed oxycodone (vs 62% in POINT), 17% prescribed morphine (vs 15% in POINT), 21% prescribed fentanyl patches (vs 15% in POINT) and 24%

buprenorphine patches (vs 21% in POINT). Although we cannot be sure that all the opioid customers recorded by these pharmacists had been taking these opioids for chronic pain and for 6 weeks or more, the similarity in these demographic and opioid prescription characteristics is reassuring. Another limitation is the potential biases that might be introduced by the reliance on self-report data. However, we used a well validated structured diagnostic clinical interview to ascertain symptoms of opioid dependence. Self-report of substance use behaviours is also reliable when confidentiality is assured and there are no disincentives for being honest,55, 56 as was the case in this study.

Contributors

LD, GC and RB conceived the study. All authors had input into the analytic plan; GC and RB undertook analyses. LD led the writing of the initial draft, and GC and RB added in sections. All authors critically reviewed and contributed to the writing of the manuscript.

Declaration of interests

SN, NL, RB, GC, BL, and LD have all been one or more of: investigators for untied investigator-driven educational grants funded by Reckitt Benckiser for post-marketing surveillance studies of buprenorphine–naloxone tablets and film, development of an opioid-related behaviour scale, or a study examining the uptake of opioid substitution therapy among chronic non- cancer pain patients. NL, RB, BL, and LD have received an untied educational grant from Mundipharma for post-marketing surveillance studies of reformulated OxyContin. MC has received payments from Mundipharma for preparation and presentation of educational material.

Acknowledgments

This study received funding from the Australian National Health and Medical Research Council (NHMRC; 1022522). LD, BL, SN, and WH are supported by NHMRC research fellowships (1041472, 1073858, 1013803, and 569738, respectively). The National Drug and Alcohol Research Centre (NDARC) at University of New South Wales (Sydney,

Australia) is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund. We thank POINT participants who were willing to share their experiences with us. We thank Bianca Hoban, Ranira Moodley, Kimberley Smith, Jessica Belcher, Sarah Freckleton, Anika Martin, and Rachel Urquhart-Secord from the NDARC for their contribution to data collection. We thank Mary Kumvaj, NDARC archivist, for her work in developing the logic for and carrying out the systematic literature search. We thank the Pharmacy Guild of Australia, the

New South Wales Pharmacy Guild, and Pain Australia, for their support of this study and assistance with dissemination. We also thank the POINT advisory committee for their advice on the design and conduct of the study.

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