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A meta-analysis based on diffuse definitions and mixed quality literature is not a good fundament for decisions on treatment of chronic pain patients

Letter To Editor:

Vowles et al.[6] attempted to quantify opioid dependence–related risks in their article "Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis." Given that the authors pooled studies with widely differing definitions, outcome variables, and populations, it is not surprising that they were unable to come to any meaningful conclusions about the risks and benefits of opioid use. Two earlier reviews that have adopted more rigorous approaches and were able to develop useful information to guide policy and medical practice in this area were not cited. Specifically, Noble et al.[5] found much lower rates for "abuse" and "addiction." In a Cochrane review, Minozzi et al.[4] intended to conduct a meta-analysis but had to reject all publications on the matter because they did not meet their quality criteria. Instead, they developed an insightful literature review. In contrast, Vowles et al.[5] included not any less than 38 studies in their meta-analysis and many of these had been rejected by Minozzi et al.[4] on their determination that the studies were not adequate for the purposes of a meta-analysis.

Vowles et al.[6] provide definitions for misuse, abuse, and addiction, which deviate from what is generally understood by these terms. This creates confusion and is a potential source for misinterpretation. The authors define "misuse" as opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects. This is identical to what is generally called "patient noncompliance," a common problem in any treatment including pharmacological treatment. Therefore, putting a figure on noncompliance (or misuse) among opioid analgesic patients only makes sense if comparing this rate to patient noncompliance for all medicines. DiMatteo[2] found in a large meta-analysis a noncompliance of 24.8%.[4] When we compare this with the misuse rates found by the authors, varying between 21% and 29%, we conclude that misuse or noncompliance among patients who use opioid analgesics is not any different from noncompliance among the general population of patients who use medicines.

Although the authors define misuse and abuse separately and differently, in the Results section, they use both terms interchangeably and it is not clear whether they report rates for abuse, misuse, or both. Their analysis of addiction is even worse. They define addiction as a "pattern of continued use with experience of, or demonstrated potential for, harm (eg, impaired control over drug use, compulsive use, continued use despite harm, and craving)." The diagnostic criterion is diffuse and because the definition says "eg," we understand that other symptoms also, unknown to the reader, were included. We wonder what else this might be.

This diffuse definition of addiction makes the outcome less meaningful because it is undefined in terms of how well the diagnostic criteria from, eg, *ICD-10* (requiring at least 3 of these symptoms out of 6 at the same time during the last year) are met. Having found that patient noncompliance is at the same level as for any other medicine, our conclusion is that there is not any reason for treating patients on opioid analgesics differently from patients on any other medicine (which may be less dangerous, equally dangerous, or more dangerous than opioid medicines). This adds to the conclusions of Minozzi et al.,[4] who concluded that the present data on the incidence and prevalence of dependence following the prescription of opioids to treat chronic and acute pain cannot be considered conclusive and that the available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence. Similarly, Noble et al. concluded that there is evidence for clinically significant pain relief provided by opioids (albeit weak evidence by their rigorous criteria) and that serious adverse events including iatrogenic addiction are generally rare in "well-selected" patients.

Vowles et al.,[6] along with Minozzi et al.[4] and Noble et al.,[5] agree that the overall heterogeneity of study methods and definitions as well as the limitations of many reports with respect to what variables they measure and report and how they analyze their data make it difficult to draw more definitive conclusions. Nonetheless, as reviews such as those performed by Minozzi et al.[4] and Noble et al.[5] demonstrate, there is an evidence base that can be used to guide rational policies, appropriate access to pain-relieving medications, and assessment of risks. Such information is relied upon by the World Health Organization,[7] British Pain Society,[1] the U.S. Institute of Medicine,[3] and other organizations in their recommendations for pain management involving opioids.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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On the importance of clear comparisons and a methodologically rigorous empirical literature in evaluating opioid use in chronic pain: a response to Scholten and Henningfield

Reply:

Thank you for the opportunity to respond to the letter of Scholten and Henningfield.[7] Fundamentally, we find ourselves in agreement with much of what they write. In fact, let us reiterate the primary finding of our review: The literature on rates of problematic opioid use in chronic pain is not in a healthy state. Not only there is vast heterogeneity in estimates of problematic use of opioids, this literature also suffers from inadequate reporting of basic demographic and pain-related characteristics. There is clearly room for improvement, ideally through careful study design, assessment and analysis of problematic opioid use, and use of specific endpoint assessments.

In their critique, Scholten and Henningfield unfortunately fail to note the important differences between our work and that of Noble et al.[5] and Minozzi et al.[4]; they also fail to report full details of these previous reports. It is relevant to highlight these issues to ensure that accurate and clear comparisons are made, as these are most likely to be of use to the scientific enterprise.

The meta-analysis by Noble et al.[5] was primarily concerned with the longer term effectiveness of opioids and adverse events related to opioid use. It included 3 types of opioid administration (oral, transdermal, intrathecal), with the latter 2 comprising just over 50% of included studies. In contrast, our review focused solely on opioids administered orally, based on the frequency with which they are prescribed in clinical practice. Thus, comparisons between the 2 reviews are likely confounded. Importantly, of the 26 studies reviewed by Noble et al., only 2 (7.7%) reported rates of opioid addiction and those authors imputed (page 8) an addiction rate of zero in the other 24 studies (92.3%). Although there is clear utility in their broader findings, we would urge caution in assuming absence of any particular phenomenon simply because it is not reported.

Second, Minozzi et al.[4] included acute cancer, headache, and noncancer/nonheadache chronic pain in their review; we reviewed only studies from the latter category. Minozzi et al. also included studies using any route of opioid administration. Furthermore, the findings of Noble et al.[5] were included in problematic use calculations. While drawing comparisons between our findings and those of Minozzi et al. is consequently bound to be imprecise and unsound, the reported incidence range of "dependence syndrome," 0%-24%, was similar to our reported range of opioid addiction, 3%-17%.

Scholten and Henningfield take particular umbrage with our definitions of misuse, abuse, and addiction. There are 3 considerations. First, these definitions were taken, almost verbatim, from statements of the ACTTION[8] (page 2289) and IMMPACT[6] (page 2326) groups. Second, Scholten and Henningfield note a preference for "patient noncompliance" rather than our term of "misuse" -given their note that these terms have *identical* definitions, their criticism seems distinctively semantic and thus is not likely to produce useful and productive scientific discussion. Third, in relation to our definition of addiction, Scholten and Henningfield note that the *ICD-10* provides a more adequate definition. Harmful consequences are clearly noted as a criterion for dependence syndrome by the *ICD-10* and for substance use disorder by the *DSM-V*. Consistent with the extant literature, we assume that tolerance and withdrawal in relation to opioids will occur with prolonged use,[1] meaning that harm likely represents a key distinction between expected natural consequences of protracted use and significantly problematic or harmful use. Therefore, classifying the most severe form of problematic use as addiction (opioid use associated with actual, or marked potential for, harm) still seems appropriate.

The second, more minor, area of disagreement pertains to the point that we used misuse and abuse interchangeably when providing results. We see one instance where abuse was used instead of misuse (page 572, second line). Although that is clearly an error in need of correction, it hardly constitutes "interchangeable" use. It seems possible for readers to spot the error and infer the intended meaning.

There are 2 final points. First, clinical guidelines consistently note the weak and/or limited evidence base for opioid use in chronic pain[5] (American Pain Society/American Academy of Pain Medicine,[3] British Pain Society[2]). The deficiencies in the problematic opioid use literature are not helped in any way by a problematic evidence base evaluating effectiveness. Clearly, this area is in need of focused attention and improvement. Second, we agree that opioid use is not *inherently* risky,[9] most patients seem to use opioids without misuse or addiction,[10] and access to *effective* interventions (including pain-relieving medications, but also including rehabilitative interventions aiming to restore effective functioning) is paramount.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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