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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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