Editorial Commentary

Effects of smoking on pain intensity in patients with chronic pain: are there clinical implications?

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The association between smoking and the presence of chronic pain is well established, and consistently found in studies that span various times and geographic locations (1-7). Less reported is the association between smoking and pain intensity (8). The recent publication by Khan *et al.* (9) provides a statistical analysis of a large sample of patients seen at a tertiary chronic pain center, providing further insight on the relationship between smoking and pain intensity. The authors are to be commended on leveraging such a large amount of data from an institutional registry over a period of nearly 5 years. Using robust statistical analysis, the authors concluded that "patients with chronic pain who smoke have worse pain, functional, sleep, and psychological and mood outcomes compared with nonsmokers. Smoking also has prognostic importance for poor recovery and improvement over time".

The overall health benefits of not smoking as well as a smoke-free environment are universally accepted (10,11). Any information that furthers our understanding of the adverse effects of smoking is helpful from a public health perspective. Such information may also lead to better treatment of smoking and its associated health problems. With that in mind, there is value in putting the findings of Khan *et al.* into clinical context (9).

Khan *et al.* note that the prevalence of smokers within their patient cohort to be 9.25%, similar to the cited smoking prevalence in California of the general population of approximately 10% (9). Smoking and pain is most established in research through population studies demonstrating that the presence of smoking increases the risk of an individual experiencing pain (1-7). Based on this, it is interesting that the incidence of smoking within their cohort of chronic pain patients was not higher than that of the general population. Other findings within demographics of this cohort were the relatively low prevalence of "history or depression" and "history of anxiety", both of which have been associated with the presence of chronic pain (12-15). Higher levels of education that may be typically expected in a chronic pain patient population were also seen in this study. This most certainly reflects the referral patterns of the clinical as well as regional demographics. However, these differences in their patient population may limit the external validity of the data to other regions or chronic pain clinic patient populations.

Quantitatively, the results must also be put into clinical context. The mean in "pain intensity now" at time 1 was 6.09 in smokers and 4.89 in non-smokers, with a mean difference of 1.2. While concepts of minimally clinically important difference (MCID) and minimal detectable change (MDC) are best suited to look at within group changes, the concept still applies in the analysis of this data. A cited value for MCID on the NRS scale is 2 (16) and similarly, greater than 1.5 is most commonly cited as the MDC (17-19). The interpretation of this is that for a

given patient, a difference of less than 2 is not significant to the patient and a difference of less than or equal to 1.5 is not reliably detected on the NRS. These concepts are particularly applicable to this study, given that while a statistical difference between groups exists, whether or not these effects are clinically relevant is less clear. Intuitively, we understand this as physicians; most of physicians would most likely approach a patient who was reporting a NRS score of 5 versus a NRS score of 6 similarly, if not the same. Conversely, the patient's perceived pain severity of a reported NRS score of 5 versus 6 is also likely similar if not the same. This importance of distinction between clinical significance and statistical significance is apparent in Khan *et al.*'s study. The difference between groups for all other measures is less pronounced than the difference in "pain intensity now". The difference between groups for "pain intensity worst" is 0.8 and for "pain intensity average" only 0.91 at time 1. For the other measures wherein a single standard deviation is represented by a difference of 10, the differences are even less pronounced: 0.01 for PROMIS pain interference, 1.93 for "PROMIS pain behavior", 3.55 for "PROMIS depression", 3.08 for "PROMIS anxiety" and so on. While a true difference exists statistically, how these patients present clinically may be the same; the statistical differences seen may be indistinguishable to both the patient and the physician.

The concepts of MCID and MDC hold more true across time within a group. Again, looking at "pain intensity now", the improvement in VAS in the smokers group went from 6.09 to 5.93 for a difference of 0.16, compared to the nonsmoker group which went from 4.89 to 4.61 for a difference of 0.28. In neither group was the change across time clinically meaningful. Similarly, the difference between the change in time in smokers compared to nonsmokers on "pain intensity now" of 0.12 (0.28–0.16) is most certainly not clinically meaningful. In fact, in most clinics in which NRS is collected in a more ordinal fashion versus a continuous measure, both groups were likely to be grossly recorded as a difference of "0". Similarly, with other measures the difference in the change between groups from time 1 to time 2 was even less: "pain intensity worst" −0.42 in smokers versus −0.44 in nonsmokers, +0.8 PROMIS pain interference in smokers versus −0.12 in nonsmokers, and +1.8 versus +0.8 in PROMIS anxiety respectively. While the authors concluded positive smoking status was associated with poor recovery and improvement over time, the difference between groups in the change from time 1 to time 2 is well below the threshold for what would be perceptible to the patient or treating physician. This conclusion by the authors, despite the many strengths of this study, should likely be received with caution and warrants further research before this conclusion can be made with confidence.

The data from time 1 to time 2 also is revealing in the overall lack of improvement in both the smokers and nonsmokers by essentially all outcome measures. Given the nature of patients with chronic pain, this is not necessarily surprising. In the context of this discussion however, it does point to the fact that to detect a difference over time between groups within a chronic pain patient population likely requires a greater follow up period than the 6 to 8 weeks that were represented by the initial visit and first follow up visit as demonstrated in this study. As the authors pointed out, "our results are limited to the first 2 patient visits, which may not capture the benefits achieved from certain interventions".

Another issue to keep in mind when interpreting the results of the study is related to the statistical modeling that was performed. In using propensity-weighting the authors are trying to evaluate the average causal effect of smoking, by accounting for "selection-bias effect" (i.e. accounting for other factors or covariates beside smoking status) of smokers *vs.* non-smokers in order to provide evidence for independent effects of smoking status. These included "included age, sex, body mass index (kg/m^2), depression and anxiety history, ethnicity, alcohol use, marital status, receiving disability, and highest educational attainment". However, as the authors recognize the "presence of confounding cannot be excluded". The authors astutely point out that not all known covariates may have been accounted for "such as concomitant substance abuse". It is also important to note that the list of covariates is highly dimensional, i.e., reflects a number of different factors, with some that are yet known. More importantly, the data should be interpreted with the understanding that the patient cohort in the study had covariate prevalence rages different than what is found in national data sets; hence this difference must be accounted for when trying to infer the results of the propensity-weighting analysis to other patient cohorts.

Irrespective of the issues above, the conclusions raised by the authors include many important and valid points. Firstly, smoking status should be assessed in patients with chronic pain. Research to this point continues to support the hypothesis that the relationship between smoking and pain may be bidirectional. Because of this potential

bidirectional relationship, it is entirely unclear that promoting smoking cessation will in fact result in lesser pain intensity in chronic pain patients who smoke. In fact, as the authors note, there are studies that suggest the contrary, with findings that pain may actually worsen (20). While smoking cessation is still generally recommended, future research should focus on how this can be best accomplished in patients with chronic pain. Additional research is also needed to investigate whether or not smoking cessation is a means of mitigating chronic pain over the long term, even if there is an apparent short-term exacerbation. Lastly, given the paucity of research on pain intensity and smoking status, combined with this study's novel findings that demonstrate significant statistical findings that are of much less robust clinical significance, additional research on this particular relationship is also warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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