*Authors' Response*

# When You Come to the Fork in the Road, Take It! Future Research into Chronic Pain as a General Condition

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The six papers in this volume investigate five common chronic overlapping pain conditions (COPCs), assessing their cross-sectional associations with six biopsychosocial domains: epidemiologic considerations; clinical pain attributes; psychologic functioning; pain sensitivity; health conditions; and measures that are putatively specific to temporomandibular disorders (TMD), one of the COPCs. A key question is whether variables within each domain are consistently associated with all five COPCs, thereby representing overlapping risk factors and implying the presence of a single centralized pain disorder. The preceding commentaries have reached different conclusions and constitute a rich debate on the merits of "splitting vs lumping" pain conditions that are conventionally held to be distinct. This debate is healthy: If there is evidence that a single centralized pain disorder is responsible for several COPCs, "lumping" those COPCs in future research studies would be valuable. Conversely, absent such evidence, COPCs should be very carefully "split" to avoid misclassification bias. In this response, we add our perspective regarding the debate.

LeResche and von Korff are critical of research diagnostic criteria in general, including those used in OPPERA, and recommend instead that "a brief assessment of anatomically defined COPCs may be sufficient for many research purposes." Such an assessment would focus attention on the person with pain rather than the particular pain condition within the person. Similarly, brief assessments—and their sufficiency—would appear to be essential if the hopes of Stohler are to be realized through "big data" methods to study TMD and other types of chronic pain. In contrast, Svensson and Exposto suggest that further subtyping of the individual COPCs is essential to determine if these OPPERA findings generalize sufficiently to subtypes of each COPC. This theme of subtyping is further clarified by Benoliel, who asserts that further studies of reductive phenotypes are essential before investigating combinations of pain disorders. In summary, the brief assessments of pain required for LeResche and von Korff and for Stohler appear antithetical to the views of Svensson and Exposto and of Benoliel, who instead demand finer phenotypic descriptions of each condition.

A prescient question arising from this debate is what actually constitutes a "disorder." One definition is "a causally relatively isolated combination of physical components that is (a) clinically abnormal and (b) maximal, in the sense that it is not a part of some larger such combination."[1] The second criterion demands knowledge of a pain mechanism that constitutes "some larger such combination." Svensson and Exposto, as well as Benoliel, point to the necessity of understanding the mechanism at the disorder level (which would justify splitting), while LeResche and von Korff, and ultimately Stohler, point to the necessity of understanding mechanism at the person level (which would justify, if not require, lumping). These contrasting conclusions mirror long-standing and legitimate differences in the field: Should we measure general or specific phenotypes? Should we lump or split case classifications? Should our focus be broad or narrow? Perhaps these individual questions can be lumped (pun intended) into the question of what is the consequence of choosing one level at the expense of the other?

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We suggest that lumping vs splitting is a false dichotomy, and that researchers should instead take the advice implicit in Yogi Berra's admonishment: "When you come to the fork in the road, take it!"[2]

The choice is not mutually exclusive: General assessments are appropriate for some research questions, whereas precise case classifications are needed for others. Future research should choose the approach best addressing the research question. For example, brief assessments—essential for large population studies—provide the only way to monitor trends and evaluate associations in nationally representative populations.[3] In contrast, the phenotypic heterogeneity inherent in brief assessments is of concern in genome-wide association studies of TMD because, in principle, heterogeneity reduces statistical power to replicate findings.[4] Nonetheless, it may be instructive to learn from research on the genetic basis for obsessive-compulsive disorder (another brain-based disorder), where both increased homogeneity and increased heterogeneity were considered viable pathways for discovery of genetic associations.[5,6] In general, we believe that studies targeting the person level (ie, by "lumping" pain conditions) can benefit by collecting data pertinent to the disorder level because pain is multidimensional.

While we agree with LeResche and von Korff regarding the limitations of any pain disorder classification with respect to reliability and validity, those limitations hold for many established classifications outside the pain field as well. Furthermore, those two properties are not sufficient to judge the overall clinical utility of any classification system. For example, revisions made to what is now the third edition of a comprehensive headache classification system[7] are validated, in part, on the utility of the classification in determining specific treatments for specific headache types. Is it sufficient to generalize that history to other pain conditions (eg, to support distinguishing myalgia from arthralgia within the TMD), thereby warranting more necessary research on types? Both levels are needed in clinical practice and in research on pain conditions. Nonetheless, we agree wholeheartedly with LeResche and von Korff that development of research diagnostic criteria must not become an end in itself, and instead a different form of attention must be given to further assessment of validity (prediction of outcomes, differential response to treatment, differences in risk factors, and causal mechanisms) of the DC/TMD.

Size matters! If a study's goal is to assess unique features of clinical subtypes of pain, it can be extremely difficult to recruit sufficient numbers of subjects with subtype permutations for rigorous statistical analysis. For example, among the 182 OPPERA TMD cases reported in this volume, 3 had arthralgia without myalgia, 31 had myalgia without arthralgia, and the remaining 148 had both arthralgia and myalgia. Svensson and Exposto appear to suggest that subtyping and exploration, despite nonexistent statistical power, is nevertheless critical. We take the opposite view: A larger sample using reliable and valid methods, such that the phenotype is explainable and reproducible, of two disorders that are more similar in key characteristics (eg, hyperalgesia) than they are different (muscle vs joint), will likely provide more reliable results compared to using a very small sample of arthralgia-only that has little statistical power and generalizes poorly to clinical settings where arthralgia-only rarely occurs. Splitting without sound theory regarding the important distinctions is more likely to produce spurious results from analyses.

Studies of specific subtypes of chronic pain face additional constraints when prospective cohort study designs are undertaken, as advocated by reviewers. Substantial resources must be invested in examiner training and calibration,[8] but that investment may be eroded by turnover of research personnel. Hardware and software used for data collection at baseline are inevitably replaced or "upgraded" after a few years, which can introduce new errors in follow-up data collection, as occurred with our assessment of headache subtypes in OPPERA-2. Research diagnostic criteria for all four of the other COPCs assessed in both OPPERA-1 and OPPERA-2 changed in the decade or so of OPPERA studies, inviting criticism that the results were outdated or at least not innovative (see Svensson and Exposto). One solution is to establish common data elements, a challenging task that requires researcher experience,[9] demonstrated outcomes,[10] and consensus[11] within a field, as demonstrated by the Diagnostic Criteria for TMD (DC/TMD)[12] and back pain research recommendations.[13] If something as ambitious as a life-course study is to be undertaken, researchers will have to confront these realities, which may require that they settle for more global assessments that can be reliably re-evaluated, even decades later.

Clinical decision-making and analysis of research data need to explicitly embrace a "variance accounted for" model with regard to local vs generalized conditions in order to weigh relative contributions to condition-specific or general outcome measures. Our data clearly point to unique variance attributable to the local condition, whether it be reports of pain (see Ohrbach et al) or measures (whether self-report or objective) specific to the target disorder (see Sharma et al). Does the existence of potential subtypes not classified (eg, medication overuse headache, within the headache domain) threaten the internal validity of the present findings? The question is of general importance: How granular does one need to go in

classification when there is a lumped category that dominates explained variance such that the assumed heterogeneity is acting in a sufficiently homogenous manner? While probing further into types (splitting) may yield important insights (eg, discovery of a medication that is specific for only cervicogenic headache),[14] how many ineffective or harmful treatments have been provided due to provider persistence in probing for the "real" subtype of a pain disorder? Patient stories point to considerable suffering and lifelong prolongation of TMD when levels of analysis regarding local vs generalized conditions are ignored and treatment is directed toward only the assumed subtype.[15]

Big data has, indeed, made big promises. But already we've seen high-profile failures to deliver.[16,17] We worry that the enthusiasm and technological capacity to compile large amounts of data seem to be advancing much more rapidly than the pace at which patient-relevant research questions are being formulated. Equally important, should Stohler's "new map" embrace and add to the multiple biopsychosocial variables (including those reported in this volume) known to exert strong influences on chronic pain? Or should the "new map" begin with a blank canvas, vacuuming up a trove of variables precisely because they have not been studied previously? Or should the "new map" bridge the gap between well-designed observational and clinical studies that address the caveats of big data (eg, confounding and efficacy) and real-life data points that address the caveats of observational and clinical studies (eg, cost, effectiveness, safety, rare clinical events, drug tolerability, ease of use, and implementation of treatments in daily clinical practice)? Perhaps that choice is another false dichotomy: LeResche and von Korff suggest a way forward by highlighting important topography to be incorporated into such a map when addressing patient-relevant research questions that might be addressed with big data.

In summary, each of the COPCs evaluated in these OPPERA papers can occur as a local condition and as part of a centralized pain condition. Clinical and research studies of these conditions should therefore utilize an appropriate multi-axial assessment and classification approach (eg, DC/TMD,[12] AAPT-TMD,[18] AAPT[19]). To lump or to split depends on the objective of the research study or the particular focus of a clinical treatment. The debate in these commentaries highlights features applicable to all such studies: pain is the dominant symptom; reductive and integrative concepts can coexist; and the public health imperative to alleviate chronic pain,[20] including TMD pain,[15] is a pressing matter.

## References


1. Scheuermann RH, Ceusters W, Smith B. Toward an ontological treatment of disease and diagnosis. Summit Transl Bioinform 2009;2009:116–120.
2. Berra Y, Kaplan D. When You Come to a Fork in the Road, Take It: Inspiration and Wisdom From one of Baseball's Greatest Heroes, ed 1. New York: Hyperion, 2001.
3. Slade GD, Sanders AE, By K. Role of allostatic load in sociodemographic patterns of pain prevalence in the U.S. population. J Pain 2012;13:666–675.
4. Smith SB, Parisien M, Bair E, et al. Genome-wide association reveals contribution of MRAS to painful temporomandibular disorder in males. Pain 2019;160:579–591.
5. Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive–compulsive disorder: An integrative genetic and neurobiological perspective. Nat Rev Neurosci 2014;15:410–424.
6. Miguel EC, Leckman JF, Rauch S, et al. Obsessive-compulsive disorder phenotypes: Implications for genetic studies. Mol Psychiatry 2005;10:258–275.
7. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
8. Bair E, Brownstein NC, Ohrbach R, et al. Study protocol, sample characteristics, and loss to follow-up: The OPPERA prospective cohort study. J Pain 2013;14(12 suppl):T2–T19.
9. Sheehan J, Hirschfeld S, Foster E, et al. Improving the value of clinical research through the use of Common Data Elements. Clin Trials 2016;13:671–676.
10. Slade GD, Ohrbach R, Greenspan JD, et al. Painful temporomandibular disorder: Decade of discovery from OPPERA studies. J Dent Res 2016;95:1084–1092.
11. Dworkin RH, Allen R, Kopko S, et al. A standard database format for clinical trials of pain treatments: An ACTTION–CDISC initiative. Pain 2013;154:11–14.
12. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for clinical and research applications: Recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache 2014;28:6–27.
13. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on research standards for chronic low back pain. Spine (Phila Pa 1976) 2014;39:1128–1143.
14. Sjaastad O, Fredriksen TA, Pfaffenrath V. Cervicogenic headache: Diagnostic criteria. Headache 1990;30:725–726.
15. National Academies of Sciences, Engineering and Medicine. Temporomandibular Disorders: Priorities for Research and Care. In. Washington, DC: National Academies, 2020.
16. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020;382:2582.
17. Mehra MR, Ruschitzka F, Patel AN. Retracted: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Lancet 2020;S0140-6736(20)31180-6.
18. Ohrbach R, Dworkin SF. AAPT diagnostic driteria for chronic painful temporomandibular disorders. J Pain 2019; 20:1276–1292.
19. Fillingim RB, Bruehl S, Dworkin RH, et al. The ACTTION-American Pain Society Pain Taxonomy (AAPT): An evidence-based and multidimensional approach to classifying chronic pain conditions. J Pain 2014;15:241–249.
20. Institute of Medicine (U.S.). Committee on Advancing Pain Research, Care, and Education. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. Washington, DC: National Academies, 2011.