

## At the Crossroads of Chronic Overlapping Pain Conditions and Research Diagnostic Criteria: Which Direction to Take?

### Guest Editors

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The initial Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) studies investigated risk factors for, clinical manifestations of, and potential causal mechanisms involved in painful temporomandibular disorders (TMD) in large convenience samples of persons without TMD ( $n = 3,258$ ) and among examiner-verified cases of TMD seeking care in the same population ( $n = 1,088$ ). These samples were assessed cross-sectionally and longitudinally to identify risk factors for TMD onset and predictors of long-term TMD outcomes. In addition to other important results, the initial OPPERA studies found that among the strongest predictors of onset of TMD were the number of other health conditions (whether painful or nonpainful), as well as the number and frequency of somatic symptoms.<sup>1</sup> These results suggested that TMD may be related to other specific symptomatic conditions or to an underlying factor associated with vulnerability to such conditions.

Eight years later, OPPERA-2 contacted persons from the original cohorts who remained enrolled in OPPERA and willing to participate in further research ( $n = 655$ ) to conduct comprehensive evaluations of five chronic overlapping pain conditions (COPCs). The overarching aim of OPPERA-2 was to compare risk factors and clinical manifestations of the five COPCs to understand features that were specific to a particular COPC and factors that the COPCs shared in common. As reported in this supplement, OPPERA-2 yielded important findings about COPCs: Slade et al report that COPCs were substantially more common when reported by assessing anatomically defined pain using a body manikin than when each COPC was assessed according to research diagnostic criteria (RDC). Ohrbach et al found that diverse measures of pain intensity and impact increased in a gradient with number of COPCs whether they were assessed by anatomical report or according to RDC. Greenspan et al show that the number of COPCs were associated with quantitative sensory testing measures of pain sensitivity across multiple

modalities, including blunt pressure pain, mechanical pinprick pain, and thermal heat pain. Sharma et al report that a number of TMD clinical findings (eg, pain-free range of jaw opening, jaw muscle palpation pain, global jaw limitation) are frequently present among persons with other COPCs, even those without a formal diagnosis of TMD, and increase with number of COPCs whether assessed by RDC or by anatomical report. Sanders et al report that manifestations of sleep disorders increase markedly with number of COPCs whether assessed by RDC or by anatomical report. And, finally, the outstanding paper by Fillingim et al indicates that measures of somatic symptom burden showed the strongest associations with individual COPCs and with number of COPCs, while negative mood, perceived stress, and pain catastrophizing were also increased among persons with multiple COPCs. In combination, these papers report, by far, the most comprehensive biopsychosocial assessment of COPCs conducted to date.

The wealth of research findings reported in this special issue of the *Journal of Oral & Facial Pain and Headache* have important implications for future epidemiologic, health services, and clinical research on chronic pain.

First, these OPPERA-2 studies of COPCs, in tandem with research carried out over the prior three decades, firmly establish that clinical and epidemiologic research on specific chronic pain conditions cannot ignore coexisting chronic pain conditions. It is now well established that the extent of COPCs is at least as important in determining prognosis, response to treatment, and health impact as the characteristics of any specific chronic pain condition. This means that COPC assessment needs to be incorporated into all clinical and epidemiologic studies of specific chronic pain conditions. Without assessment of co-occurring COPCs, risk factors and manifestations of a specific chronic pain condition cannot be differentiated from general risk factors and manifestations of centralized chronic pain.

Second, given the extent of comorbid chronic pain conditions—particularly among persons with high-impact chronic pain—clinical, epidemiologic, and health services research on chronic pain as a general condition is a critically important and neglected line of research. This means that rigorous research standards will need to be developed for research concerning co-occurring COPCs.

An implication of these two observations is that we will need to develop practical, efficient approaches to studying specific chronic pain conditions while adequately assessing overall chronic pain status, including assessment of comorbid COPCs—whether the COPCs are the primary object of investigation or contextual factors in research concerning a specific chronic pain condition.

Research on chronic pain followed the lead of psychiatry in developing RDC. When RDC were developed for specific chronic pain conditions, including orofacial pain conditions, headache, fibromyalgia, irritable bowel syndrome, and others, it was hoped that more refined diagnostic classification would yield new insights into risk factors, effective treatment, and prognosis. Unfortunately, this promise has for the most part not been realized. In the case of mental disorders, it has recently been observed that development of RDC became an end in itself and an obstacle to identifying causal mechanisms and more effective treatments.<sup>2</sup> This led the National Institute of Mental Health to place a moratorium on research funding for development or evaluation of mental disorder RDC.<sup>3</sup> The findings reported here regarding COPCs as defined by RDC, contrasted with findings based on simpler assessments using body manikins or self-report of bodily symptoms, provide an opportunity to consider the role that RDC for chronic pain conditions should play in future epidemiologic and clinical research.

OPPERA-2 findings demonstrate the need to adequately assess comorbid chronic pain conditions in most, if not all, clinical, epidemiologic, and health services research studies of specific chronic pain conditions. A key question then is when and whether RDC assessment for each comorbid chronic pain condition is useful. The OPFERA-2 findings suggest that brief assessment of anatomically defined COPCs may be sufficient for many research purposes. Moreover, it is time for a critical assessment of whether RDCs for specific chronic pain conditions are, in fact, contributing to advances in understanding of causal mechanisms and identification of more effective treatments and preventive measures.

RDC have utility for research and clinical practice when they are consistently found to have clinical validity by: (1) improving prediction of patient outcomes; (2) predicting differential response to

specific treatments that improve patient outcomes; (3) identifying replicable differences in risk factors by differential diagnosis; and (4) elucidating biologic, psychological, or behavioral causal mechanisms that lead to advances in treatment or prevention. Applying these criteria, the performance of RDC for common chronic pain conditions has not been impressive to date. Differentiation of tension-type headache and migraine is one of the better-supported differential diagnoses, with specific, effective treatments identified for tension-type headache and for migraine. However, whether these two headache disorders are distinct or represent different points on a continuum of headache severity remains unsettled.

RDC for irritable bowel syndrome have been helpful in research concerning potential causal mechanisms and in avoiding inappropriate treatments, but clinical validity of irritable bowel syndrome RDC has not been definitively established. Research on the clinical validity of fibromyalgia RDC has generally yielded disappointing results. RDC for TMD, which we helped develop, provided the field with a badly needed standardized diagnostic language and helped launch research that dispelled aggressive and ill-advised treatments for chronic orofacial pain. Later studies published in this journal<sup>4</sup> assessed the RDC against the standard of expert clinical opinion based on comprehensive clinical (including radiologic) information and led to the development of revised clinical criteria (The Diagnostic Criteria for TMD [DC/TMD]).<sup>5</sup> However, the clinical validity of these criteria has yet to be established in terms of predicting outcomes, differential response to treatment, replicable differences in risk factors, and elucidating causal mechanisms. It is past time for a rigorous and sober assessment of the extent to which the RDC/TMD, and RDC for other common chronic pain syndromes, are yielding the hoped-for advances in treatment, prevention, and elucidating causal mechanisms.

Similarly, it is now well established that persons with multiple chronic pain conditions or diffuse chronic pain differ in important ways from persons with a single chronic pain condition or localized chronic pain. Repeatedly demonstrating that persons with multiple chronic pain conditions have less favorable responses to treatment, less favorable prognoses, and are more likely to have high-impact chronic pain will not advance understanding of the causes, treatment, and prevention of chronic pain.

OPFERA-2 findings suggest the need for new approaches to assessment of specific chronic pain conditions and chronic pain in general that shed light on the hypothesized central chronic pain mechanisms. For example, research employing functional MRI or connectivity analyses might contrast central pain processing in persons with a specific chronic

pain condition with vs without COPCs. Such research could dovetail with prospective studies aimed at identifying neurophysiologic mechanisms that create susceptibility to peripheral and central hypersensitivity. Longitudinal studies of the transition from having a single chronic pain condition to having two, and from having two chronic pain conditions to having three, might be particularly revealing. Since COPCs are generally found to be more common among women, longitudinal studies of the role of sex hormones in the onset and course of COPCs are needed, particularly research that assesses multiple hormones beyond the “usual suspects” of estrogen and progesterone. Investigations of genetic and epigenetic factors among persons with a specific chronic pain condition comparing those with to those without COPCs might also be informative. Finally, life-course developmental research is needed to elucidate the roles of adverse childhood experiences and early-onset affective illness in establishing vulnerabilities to diverse COPCs.

The articles in this issue provide important foundational information for the next generation of research into COPCs. As the next generation of research is planned, there is a need for a critical evaluation of the contributions and the failures of RDC for chronic pain conditions and for theoretically coherent and rigorous methods for conducting research on COPCs.

## References

1. Slade GD, Ohrbach R, Greenspan JD, et al. Painful temporomandibular disorder: Decade of discovery from OPPERA studies. *J Dent Res* 2016;95:1084–1092.
2. Casey BJ, Craddock N, Cuthbert BN, Hyman SE, Lee FS, Ressler KJ. DSM-5 and RDoC: Progress in psychiatry research? *Nat Rev Neurosci* 2013;14:810–814.
3. Ghaemi SN. After the failure of DSM: Clinical research on psychiatric diagnosis. *World Psychiatry* 2018;17:301–302.
4. Schiffman EL, Truelove EL, Ohrbach R, et al. The Research Diagnostic Criteria for Temporomandibular Disorders. I: Overview and methodology for assessment of validity. *J Orofac Pain* 2010;24:7–24.
5. 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.