

Further Evidence for Overlaps Among Chronic Pain Conditions—But No News About Causal Relationships

Peter Svensson, DDS, PhD, Dr Odont

Section of Orofacial Pain and Jaw Function
Department of Dentistry and Oral Health
Aarhus University,
Aarhus, Denmark;
Faculty of Odontology
Malmö University,
Malmö, Sweden;
Scandinavian Center for Orofacial Neurosciences (SCON)

Fernando Exposto, DDS, PhD

Section of Orofacial Pain and Jaw Function
Department of Dentistry and Oral Health
Aarhus University,
Aarhus, Denmark;
Scandinavian Center for Orofacial Neurosciences (SCON)

©2020 by Quintessence Publishing Co Inc.

In the present papers by Slade et al, Ohrbach et al, and Greenspan et al, the authors studied how overlap of five chronic overlapping pain conditions (COPCs) influenced parameters such as clinical characteristics and pain sensitivity. The authors are to be commended for the exhaustive work done in these studies, as they help us to further understand how different COPCs appear to influence each other. The papers reported in this special issue raise opportunities for future research, but also some methodologic issues that should be considered in future research on COPCs.

An important issue that should be considered in the interpretation of the results of the present studies, as well as in future COPC research, is the role of pain medications in the development of COPCs. It is possible that sustained use of pain medication(s) plays an important role in the development and maintenance of COPCs, which is likely to confound some of the relationships reported in the present studies. It has been shown that both increased pain interference and number of pain comorbidities can lead to an increase in analgesics consumption, which in turn can lead to increased pain sensitivity and altered pain processing.^{1–3} As such, it may be that the changes in pain processing and increased pain intensity found in these studies are in part due to analgesic-medication hyperalgesia. If this were the case, the co-occurrence of common chronic pain conditions might be partially or completely explained by a common risk factor—the sustained use of pain medications that are implicated in hyperalgesia. Furthermore, the lack of medication assessment did not allow for the classification of one of the most frequent types of headaches, which is medication-overuse headache,⁴ which may cause problems in the interpretation of

the relationship between headache disorders and the other COPCs.

Limitations of the classification of headache disorders in the present studies also need to be considered. The large amount of missing data from participants regarding headache diagnosis (233 out of 655) and the lack of rigor with which headache disorders were classified limit the conclusions that can be drawn regarding headache disorders and COPCs. These issues are made clear when looking at the percentage of tension-type headache (TTH) cases in the study by Slade et al, which was reported to be 10%, whereas TTH prevalence rates from previous studies are between 63% and 87%.^{5,6} In addition, the ID-Migraine, which was used for migraine diagnosis, was validated for the original International Classification of Headache Disorders (ICHD)⁷ and has yet to be validated against the third edition of the International Classification of Headache Disorders (ICHD-3). This poses a problem because the ID-Migraine may classify as migraine what ICHD-3 would classify as probable migraine.⁷ It also does not classify chronic migraine, as this diagnosis did not exist in the original ICHD. Furthermore, the ID-Migraine has been shown to be better at ruling out migraine than ruling it in,⁸ and has better sensitivity and specificity when assessed in patients presenting with headaches in the previous 3 months,⁷ which is not the case in this population-based study. Taken together with the issues of missing data and lack of information on medication-overuse headache, there is likely to be substantial misclassification of headache disorders according to the ICHD-3 criteria in the sample. In this context, the current papers do not address the relationships of specific types of primary headaches with the other COPCs. Thus,

these papers are looking at an umbrella diagnosis of “headaches” that probably represent very different underlying pathophysiologic mechanisms; eg, migraine vs TTH.

We also wonder about the lack of distinction between myalgia and arthralgia within temporomandibular disorders (TMD) in the reported studies. It would be interesting to understand if there are meaningful differences between myalgia and arthralgia in their relationships with the other COPCs. For example, it has been demonstrated that headache disorders are more related to myalgia than arthralgia.⁹ As such, including all the patients under the “TMD umbrella” may have diluted the relationship between more specific types of TMD and specific types of headache.

Considering the above-mentioned points, in future research, it would be important to understand the extent to which a more detailed phenotypic description of COPCs using both a comprehensive classification system (such as the ICHD-3¹⁰ or the new International Classification of Orofacial Pain¹¹) and a detailed pain modulation assessment is able to explain some of the relationships among the different COPCs.

Regarding the overlap of the three musculoskeletal COPCs, we agree that there is likely an additive property when reporting pain for TMD, lower back pain, and fibromyalgia. But, it should also be considered that there could be different patient phenotypes among these diagnoses. For example, Pfau et al have shown two different types of TMD patients: one with increased pain sensitivity limited to the trigeminal system, and another that more closely resembles fibromyalgia, with increased pain sensitivity in both the trigeminal and spinal system.¹² The latter patients presented with somatosensory profiles and pain on palpation resembling fibromyalgia patients. This points to the fact that there may be different patient phenotypes, and that the amount of interaction among COPCs may be different depending on what type of phenotype is present. Furthermore, the putative underlying pain mechanisms are only discussed in terms of “central sensitization,” but an intriguing and important question seems to be how the different and overlapping pain conditions exert their mutually reinforcing action on, eg, self-reported pain intensity. The present studies nicely illustrate the phenomenology of COPCs, but more needs to be done to elucidate the underlying neurobiology.

The quantitative sensory testing (QST) protocol used in the paper by Greenspan et al employed the German Research Network on Neuropathic Pain (DFNS) protocol for mechanical cutaneous pain assessment, but the DFNS protocols were not used for the other QST measures. It has been shown that the DFNS protocol is reliable and shows very little

heterogeneity between different centers for both healthy individuals and patients with peripheral neuropathic pain,^{13,14} which renders it ideal for multicenter studies, such as the study by Greenspan et al. For the protocol used by Greenspan et al, with the exception of pressure pain threshold (PPT), we do not know what the reliability is between centers. We wonder why the present studies performed the three different tests (PPT, mechanical pain, and heat pain) in different body sites, which does not permit comparison of sensory modalities across the different COPCs. Since the investigators did not do all the modalities at three consistent sites, it does not allow comparisons between segmental and extra-segmental sites for heat pain sensitivity and mechanical pain sensitivity, which would have been important for the interpretation of pain processing between the trigeminal and spinal system for the COPCs. Perhaps there remains merit in the suggestion of a standardized description of somatosensory sensitivity, both at the painful region and in a nonpainful control region.¹⁵ Furthermore, the employed tests for temporal summation (TS) primarily target the superficial tissues, and TS measures of deep nociceptive input may be more useful for studying musculoskeletal pain conditions.

Given the duration and extent of the studies and the OPPERA project, it is not surprising that their intriguing findings raise many questions for clarification and for future research. In considering the findings, we argue that it is important to strive to achieve detailed and valid phenotypic classification of each of the COPCs in order to differentiate the effects or manifestations of specific chronic pain conditions from the generalized effects of manifestations of multiple COPCs. Obviously, classification is not the entire solution, but rather a tool to be used in clinical research. Simply put: We now need mechanistic studies to advance the understanding of underlying neurobiologic mechanisms in COPCs, with implications for management of such patients.

References

1. Voon P, Buxton JA, Wood E, Montaner JS, Kerr T. Dose-response relationship between functional pain interference and nonmedical analgesic use: Findings from a nationally representative Canadian survey. *Can J Pain* 2018;2:103–112.
2. Wasserman RA, Hassett AL, Harte SE, et al. Pressure pain sensitivity in patients with suspected opioid-induced hyperalgesia. *Reg Anesth Pain Med* 2015;40:687–693.
3. Samuelsen PJ, Nielsen CS, Wilsgaard T, Stubhaug A, Svendsen K, Eggen AE. Pain sensitivity and analgesic use among 10,486 adults: The Tromsø study. *BMC Pharmacol Toxicol* 2017;18:45.

4. Kristoffersen ES, Lundqvist C. Medication-overuse headache: Epidemiology, diagnosis and treatment. *Ther Adv Drug Saf* 2014;5:87–99.
5. Lyngberg AC, Rasmussen BK, Jørgensen T, Jensen R. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. *Eur J Epidemiol* 2005;20:243–249.
6. Stovner LJ, Andree C. Prevalence of headache in Europe: A review for the Eurolight project. *J Headache Pain* 2010;11:289–299.
7. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: The ID Migraine validation study. *Neurology* 2003;61:375–382.
8. Cousins G, Hijazze S, Van de Laar FA, Fahey T. Diagnostic accuracy of the ID Migraine: A systematic review and meta-analysis. *Headache* 2011;51:1140–1148.
9. Gonçalves DA, Camparis CM, Speciali JG. Temporomandibular disorders are differentially associated with headache diagnoses: A controlled study. *Clin J Pain* 2011;27:611–615.
10. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (ICHD-3). *Cephalalgia* 2018;38:1–211.
11. International Classification of Orofacial Pain. Resources. https://www.ihs-headache.org/binary_data/3468_the-international-orofacial-pain-classification-committee-icop-1-beta-for-review.pdf. Accessed 27 July 2020.
12. Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. *Pain* 2009;147:72–83.
13. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 2006;123:231–243.
14. Vollert J, Attal N, Baron R, et al. Quantitative sensory testing using DFNS protocol in Europe: An evaluation of heterogeneity across multiple centers in patients with peripheral neuropathic pain and healthy subjects. *Pain* 2016;157:750–758.
15. Svensson P, Baad-Hansen L, Pigg M, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions—A taskforce report. *J Oral Rehabil* 2011;38:366–394.