The Co-Occurrence of Diseases

The assumption of a single diagnosis accounting for a patient's chief complaint does not fit well within the biopsychosocial disease model,[1] nor does it fit well within the frequent observation of many disorders co-occurring with a complex index disease, such as a temporomandibular disorder (TMD).[2] The single diagnosis for a TMD-type complaint was challenged in 1992 by the biopsychosocial model–based dual-axis Research Diagnostic Criteria for TMD (RDC/TMD).[3] The RDC/TMD, by organizing physical disorders into three separate domains, permitted multiple diagnoses across more than one domain. Furthermore, the assessment of symptoms from other nonmasticatory systems using the RDC/TMD Patient History Questionnaire was intended to identify the co-occurrence of other disorders. As such, the RDC/TMD was perhaps the first diagnostic system to formally recognize TMDs as a complex disease not limited to the masticatory system.

The subsequent dual-axis Diagnostic Criteria for TMD (DC/TMD) improved upon the reliability and validity of its RDC/TMD predecessor and remains consistent with the biopsychosocial model.[4] The DC/TMD similarly uses two domains for the physical axis, permits multiple diagnoses within and across both domains, and provides a person-level assessment in order to screen for other disorders. Clearly, we are making progress in better understanding TMDs; however, with the additional information collected from a single patient, diagnosis and clinical decision-making are more challenging. A pivotal question is whether the multiple masticatory system diagnoses permitted by the DC/TMD point to discrete disorders, each of which might warrant its own treatment, or represent at varying levels of integration a central disorder requiring a yet different form of treatment. Another pivotal question concerns the co-occurrence of other disorders accompanying the TMDs, particularly if they are risk determinants for onset and/or progression of TMDs or if they might modify response to TMD-targeted therapies.

The co-occurrence of diseases, a current frontier in our science, is more complex than it initially appears. Comorbidity is the co-occurrence of two or more supposedly separate conditions that is greater than expected based on the probability of their co-occurrence in the population.[5] This definition points to many challenges. Existing medical and mental health classification systems (eg, International Classification of Diseases [ICD], Diagnostic and Statistical Manual [DSM]) do not deal with comorbidities well, perhaps because only relatively recently has comorbidity become a focal topic. Publications with "comorbidity" in the title first appeared in 1970 and began to slowly increase, with 256 publications in the period from 1986 to 1990, then rapidly increased, with nearly 6,900 publications in the last 5-year period. The inflection point in the development of the literature from 1986 to 1990 coincided with the developmental period of the RDC/TMD. Increased emphasis on comorbidity across this period may also stem from more chronic disease accompanying greater life expectancy, perhaps pointing to comorbidity as a consequence that will become increasingly more frequent.[6]

The complexity of disease co-occurrence, and in particular, comorbidity, is reflected in an equally broad range of perspectives regarding the choice of which level of complexity to consider—the focus for the remainder of this editorial. For example, the editors of this journal have research backgrounds that range from cellular to social, and we surely have correspondingly wide-ranging perspectives regarding the optimal level for investigation of disease co-occurrence. Because of complex symptomatology shared across conditions within the DC/TMD and shared with yet other conditions that are often described as comorbid with TMDs, the very definition, as well as the diagnostic criteria for the TMDs, are called into question. Much of the comorbidity research focuses on whether associations exist between the "other disorder of possible relevance" and the "disorder of primary interest"—an important topic. In a special issue of this Journal (*The OPPERA Study: Act 3*, Volume 34 Supplement, 2020), our group published a set of six papers focused on overlapping pain conditions as one aspect of comorbidity. Those papers are accompanied by four peer commentaries, each of which provides very different perspectives regarding how comorbidity should be pursued, ranging from more inclusive groupings of pain disorders to more exclusive separations of the disorders. These differing perspectives find parallels in the methodologic approaches described below. That special issue on comorbidity, using painful TMD as the index condition, represents a substantial step forward for not only TMDs, but for the pain field as a whole. But this is barely the beginning.

One overall conclusion from that special issue might be that comorbidity lies within the eyes of the beholder.

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The further inclusion of more sophisticated methods for investigation of comorbidity is clearly called for as one response to the beholder's vision. In contrast to physical disorders (eg, cardiac diseases), which have more-or-less clear(er) boundaries, mental disorders have more-or-less fuzzier boundaries (despite well-operationalized criteria),[7] and that characteristic of mental disorders gives them perhaps a more fluid role within the realm of research on comorbidity. Consequently, the considerable methodologic advances in mental disorder comorbidity research may offer substantial insights, guidance, and testable hypotheses for furthering our understanding of TMDs and their complexity, including comorbidity and the extent to which that contributes to the complexity of TMDs.

As an example (and a frequently encountered one), consider the co-occurrence of masticatory myalgia and TMJ arthralgia within the DC/TMD. Further, consider the co-occurrence of masticatory myalgia with shoulder myofascial pain or with lower back pain, both of which occur outside the DC/TMD. These pairings of disorders raise questions that are of equal importance to the clinician, who must interpret these complex relationships in a given patient for treatment purposes, and to the researcher, who is tasked with going beyond simple associations.

Those pairings of disorders may represent potential comorbidity, and while associations between two disorders can be easily tested with the appropriate statistical model, that will not be enough. Rather, any relationship between two such disorders will need to be unraveled. As viewed from mental disorder research and applied to the pain field, *apparent* comorbidity could occur due to any of: detection artifacts, such as referral patterns or screening practices; forced categorical assignment of a condition when a dimensional approach might be more appropriate; overlapping criteria among the co-occurring disorders; artificial subdivisions; disease #1 occurring as an early manifestation of disease #2; and disease #1 occurring as part of disease #2. In contrast, *true* comorbidity could occur due to: shared or overlapping risk factors; a comorbid disease pattern representing a distinct meaningful syndrome; and disease #1 acting as a risk factor for disease #2. Findings and implications for these explanations are available.[5]

These pairings may also be addressed by considering what lies outside of disease boundaries.[8] Homotypic comorbidity refers to comorbidity between disorders within a grouping, whereas heterotypic comorbidity refers to comorbidity between disorders from different diagnostic groups. These two types of comorbidity are not rigid, but rather relative. For example, are masticatory myalgia and TMJ arthralgia simply two co-occurring disorders, or are they comorbid disorders (as previously defined), no different than, say, masticatory myalgia and low back pain might be comorbid disorders? If masticatory myalgia and TMJ arthralgia are comorbid disorders, then is that comorbidity grounded in both disorders being TMDs (homotypic comorbidity), or are these two disorders only artificially linked as so-called TMDs, but in fact belong to different diagnostic groups (heterotypic comorbidity)? And, if they belong to different diagnostic groups, then what dimension defines that difference? Dimensions of relevance might include structure, nociceptive mechanism, temporal state, pain processing, or consequences.

Both homotypic and heterotypic comorbidities have specific causes identified to date.[8] Clinical snapshots are inherently cross-sectional; concurrent vs successive comorbidity of the myalgia and arthralgia may be very informative, but such a distinction clearly requires prospective studies or long-term observation of a given patient. Is the association between two disorders a basis for a particular class of disorder rather than just for the presence of comorbidity? For example, the combination of myalgia and arthralgia may represent a different disorder from either condition alone existing as "pure" disorders. But while the two "pure" disorders may exist, are the differences between them dissimilar enough? This graded interpretation will surely need to invoke the principle of parsimony. Advances in the fields of clinimetrics[9–11] and psychometrics[12–14] may help regarding diagnostic classification for pain disorders and whether a putative phenotype is homotypic or heterotypic with another disorder.

A closely related aspect of comorbidity is splitting vs lumping, which refers to how boundaries are defined between two or more potential diseases. Disease boundaries are often very much in the eye of the beholder. Should two putatively separate disorders, whether within homotypic or heterotypic comorbidity, remain separate (splitting), or can they be combined as though they are a single disorder (lumping)—whether for research purposes or for clinical care? A frequently stated concern regarding lumping is inappropriate diagnostic heterogeneity. But heterogeneity is relative to purpose. For example, a given type of intervention might be deemed relevant for a diagnostically heterogenous group in relation to a purported mechanism of action that applies to all diagnoses within the group – such that the group shares a single (lumped) diagnosis of a different type.

Splitting vs lumping might also be considered from other perspectives. Continuing with the earlier example, should co-occurrence of masticatory myalgia and TMJ arthralgia remain as split disorders, or can they be lumped? One perspective, already discussed, is to consider the basis (eg, structure, nociceptive mechanism, temporal state, pain processing,

or consequences) for a different grouping within heterotypic comorbidity. A second perspective is the justification for choosing splitting vs lumping and the corresponding concordance of methods. Strong theory, linked study aims, and descriptive statistics can justify splitting vs lumping; if these qualities are absent, then the selected approach is probably not convincing. A stepped analytic approach permits examination of the contribution of entities within the selected approach; this may include a "lumped" entity as perhaps a different disorder. A third perspective concerns statistical power and sampling considerations; "pure" arthralgia of the TMJ occurs at a low frequency, and consequently retaining it as a separate disorder may reduce statistical power for analysis. A fourth perspective concerns classification accuracy: myalgia and arthralgia can be reliably discriminated, but only with specific operationalization[15] and rigorous examiner calibration (supported by excellent examiner reliability). Otherwise, discrimination between the two disorders is poor, and splitting is neither meaningful nor interpretable. But lumping should never be selected simply as a solution for poor classification accuracy, as the results will have poor generalizability to any type of diagnostic framework. A final perspective lies within the community of science. Considerable research, including our own, has utilized the concept of "painful TMDs."[2,16] A "painful TMD," however, can represent various concepts: a grouping variable of reliable diagnostic classifications; a descriptive variable (eg, the pain-related TMD diagnoses vs the TMJ diagnoses within the DC/TMD); or a newly operationalized variable that meets the needs of the study aim. Consequently, splitting and lumping are not mutually exclusive, but rather should be regarded from multiple perspectives. The broader domain of comorbidity brings a fresh, if not needed, contrast to the dichotomy of splitting vs lumping.

The primary focus here has been to identify the need in both the clinical and research settings for more careful conceptualization of this complex topic of co-occurring diseases, comorbidity, and splitting vs lumping. A major task for a field such as comorbidity, marked less by certainty and more by nuance and ambiguity, is to implement strong methods.[17] TMDs are seldom a single isolated condition,[2] and the implications of comorbidity are immense for both the next advances in research and translation to clinical care.

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