

Chronic Pain and Depression: A Spectrum Disorder?

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Introduction: Chronic Pain and Depression

Advancing knowledge to resolve the enigma of chronic pain was a major impetus for the dedication of intellectual and technical efforts that were the focus of the congressionally declared Decade of Pain Control and Research. Yet despite these efforts, we are still confronted by a rising prevalence of chronic pain that is estimated to incur billions of dollars annually in health care (and disability compensation) costs (1). The diversity of conditions categorized under the rubric of chronic pain often creates difficulties in developing an understanding of “what chronic pain is,” and how such conditions can, and should be most effectively treated and/or managed.

In part the difficulty is that chronic pain is not a unitary disorder, but is instead the result of particular, common mechanisms that are evoked by a variety of conditions. As these neural processes of chronic pain progressively engage hierarchical brain networks, the sensory event(s) may activate neuraxes that subserve cognition, emotion and behavior. Thus, chronic pain cannot simply be viewed as durable acute pain, but rather as syndromes manifested by a diversity of signs and symptoms that are biologically, psychologically and socially expressed. Appreciating this, the International Association for the Study of Pain defines chronic pain as having “...generally... both nociceptive and neuropathic components, rather than a single cause. Psychosocial factors (cognitive, behavioral, and emotional) typically contribute to the pain experience, emotional distress, and physical disability (2).”

As this definition of pain would indicate, chronic pain is associated with major depressive disorder (MDD) (3-7). Polatin and colleagues assessed rates of chronic pain patients who met the diagnostic criteria for current or lifetime psychiatric disorders, and found that 77% of patients were diagnosable with a psychiatric disorder at some point in their lifetime (6). Over 65% of chronic pain patients met the diagnostic criteria for MDD at some point in their lifetime, and about 45% met the criteria for current MDD, as compared to 17% and 5%

of the general population, respectively (8). Although such studies demonstrated the high co-morbidity of MDD in chronic pain, these findings do not explicitly speak to causality, and the relationship between chronic pain and MDD remains unclear (9). Such ambiguity prompts the question of whether MDD is a consequence of the physiology and/or experience of chronic pain, or whether patho-etiological factors of MDD may predispose the onset and maintenance of chronic pain.

Attempts to clarify the putative relationship of chronic pain and psychopathology were provided by Gatchel and colleagues who demonstrated that the presence of psychopathology at the onset of pain was not predictive of the development of chronicity, although higher rates of MDD (in addition to substance abuse and personality disorders) were shown in chronic patients (10,3). According to Dersh, Polatin, and Gatchel, this pattern “...indicates that ...psychiatric disorders are not solely related to the onset of pain per se, but are linked with the development of chronicity (11).”

Fishbain and co-workers have reviewed 5 major hypotheses that relate depression to the development of chronicity in pain patients (12). While support for the *antecedent hypothesis* (in which depression precedes the development of chronic pain) was lacking, there is strong evidence to support the *consequent hypothesis* (i.e., depression occurs as a consequence to pain). As well, the *cognitive behavioral mediation hypothesis* (i.e., cognitions mediate the relationship between chronic pain and the development of depression) was well supported, and is generally considered to be compatible with the consequent hypothesis, as both suggest that the developmental “direction” progresses from pain to depression. The *scar hypothesis* (in which episodes of depression occurring prior to the onset of pain predispose an individual to a depressive episode after pain onset), and the *common pathogenetic mechanisms hypothesis* (which suggests that underlying genetic, and/or phenotypic substrates mediate the development and ultimate expression of pain and depression) were both



Swimmer, oil on canvas by Jon Aley

supported by findings that revealed a higher percentage of chronic pain patients had relatives diagnosed with a depressive disorder, as compared to familial patterns of pain and depression in the general population (12,11).

Banks and Kerns' stress-diathesis model integrates these various hypotheses such that pre-existing, perhaps dormant psychological characteristics of an individual are activated by the stress of the pain experience, and subsequent expression of psychological traits then serve to further exacerbate pain experience and behavioral reactivity (13,11). This is consistent with the consequent, scar, common pathogenetic mechanism, and cognitive behavioral hypotheses in that while pain precedes depression, psychopathologic predispositions increase the likelihood of developing both depression and chronicity of pain. Similarly, Gatchel has posited that "... patients whose pain later becomes chronic may 'bring with them' certain pre-morbid or predisposing psychological/personality characteristics or disorders...that are exacerbated by the stress of ... pain" (14).

While these models may account for the patterns of chronic pain and depression and/or support the possibility of a causal relationship, they do not specifically address the mechanisms that might be involved. This is an important consideration inasmuch as 1) treatment for co-morbid depression and chronic pain should address mechanism(s) by which they co-occur, and 2) the development of more efficacious therapies might be facilitated by a diagnostic framework that enables better mechanistic and practical definitions and distinctions.

The Spectrum Disorder: Concept and Utility

Dersh et al identified diagnostic issues as one obstacle to understanding the relationship between chronic pain and depression (11). They note that "...the term 'depression' has been used to refer to a mood, a symptom, and a syndrome". This reflects a key focus of our ongoing work; namely that both chronic pain and depression can manifest a constellation of signs and symptoms that may be indicative of an underlying neuropsychiatric spectrum disorder. *In a spectrum disorder, genetic and phenotypic factors predispose certain individuals to express central nervous system (CNS) vulnerabilities to neuropathological mechanisms that subsequently are manifested as neuropsychiatric features (i.e. chronic pain, somatic symptoms of mood disorders, altered sensitivity to certain pharmacologic agents such as opioids and cannabinoids, etc).*

The diagnostic difficulties inherent to classifying depression and chronic pain sustain our argument to

employ the concept of a spectrum disorder. While the biomedical paradigm enables most of medicine to validly define disorders by a particularly discrete etiological factor, psychiatry—and to some extent pain medicine—still defines a large number of disorders by their syndromes. Syndromes are typically defined according to a set of defining symptoms, not all of which must surpass sub-clinical thresholds (15). For example, depressive syndromes typically involve mood symptoms and their behavioral correlates (e.g. sadness and frequent crying or anhedonia and flat affect), and somatic symptoms (e.g. sleep disturbances, motor retardation, appetite or weight changes, loss of energy). A physician may judge a depressed patient's change in mood, affect, and energy level to be abnormal using both subjective and objective impressions.

However, diagnosis is still largely dependent upon the subjective assessment of whether something is normal or abnormal (and thus significant to the categorization as a clinical "disorder"). Symptoms that are judged to be normal because their severity is sub-clinical may actually represent significant factors which should be emphasized according to their relative contribution to the patient's overall condition. For example, sleep disturbance is a somatic symptom that is assessed as part of differentiating a particular depressive syndrome, but the frequency of episodes of insomnia required to consider it abnormal is mostly determined by subjective means, both by the patient (based on past experience), and the physician (based on clinical judgment). While one episode of insomnia a week may be considered to be normal (in general), it may be a component of underlying neuropsychiatric changes that when taken together contribute to the overall syndrome comprising depressive psychopathology. If the same argument holds true for chronic pain in depressive disorders, then a chronic pain condition may be diagnosed in addition to depression, when in fact it merely represents the exceeding of a subjective clinical threshold for the symptoms of soreness and muscle tension in a depressed patient. Additionally, the validity of psychiatric diagnoses remains a somewhat contentious issue because of the difficulty in distinguishing between disorders so as to resolve issues of co-morbidity, and the fact that these problems are further confounded by the need to differentiate between normality and abnormality for each symptom that is a component of a particular syndrome.

Although there are reasonable arguments for considering chronic pain and depression as distinct clinical entities, this may change if they are considered as neuropsychiatric syndromes of a larger spectrum disorder (11,5). Chronic

pain manifests distinguishable syndromes, depending on the particular patho-etiological basis and symptoms present. Depressive syndromes are also distinguishable (e.g., dysthymia vs MDD). However, the symptoms comprising chronic pain and depressive syndromes can overlap to create “criterion contamination” (e.g., somatic pain occurring as part of MDD, and affective symptoms in patients with chronic pain) (16). The use of certain clinical tools to diagnose depression in chronic pain patients (such as the Beck Depression Inventory (BDI)) may further contribute to this ambiguity. The BDI was “...standardized on psychiatric populations from which those with significant physical illness and disability were excluded” (11,17). Distinguishing signs and symptoms that are (co-)related to pain and/or depression may therefore be difficult using such a tool.

The spectrum disorder concept solves this problem by considering *all* symptoms to the extent that they appear in each syndrome. Symptoms are judged to be normal or abnormal by *pragmatic* factors that refer to their severity and durability (e.g., whether the symptom interferes with a patient’s daily living). As a nosological concept, spectrum disorders represent a means by which syndromes can be associated, based on the commonality of underlying patho-etologies, and overlapping presentation of clinical and sub-clinical symptoms.

Neurobiological Substrates of a Pain (-Depression) Spectrum Disorder

A spectrum disorder nosology does not invalidate the fact that chronic pain and depressive disorders—as syndromes—frequently occur without significant co-morbidity of symptoms. Nor does it conflict with the fact that even when co-morbid, the onset of depression and chronic pain do not typically coincide. Instead, the spectrum disorder suggests a more appropriate way to “ground” the occurrence of co-related signs and symptoms to an underlying patho-etiological set of factors.

As a spectrum disorder, the *form* that a disorder assumes is determined by its composite symptoms. These symptoms do not necessarily cause each other as much as co-activate each other, allowing for multiple presentations along the spectrum to be diagnostically and mechanistically associated while possibly having little

resemblance to each other. Common mechanisms may be identified as co-activating factors. Chronic pain and depression are likely to have common co-activating factors as a result of their neurophysiological overlap (5,4). These factors include shared anatomical pathways for pain and affective processes, the fact that norepinephrine, serotonin and glutamate (neurotransmitter systems most strongly implicated in the pathophysiology of mood disorders) are also involved in matrix mechanisms of pain, and the efficacy of serotonergic- and noradrenergic-specific antidepressants in treating chronic pain as well as depression (11,18-19).

To be sure, pain—as experience—can be an antecedent to negative emotional reactivity, and together, the pain-emotionality complex may evoke suffering (20). Certainly, Peter Moskowitz’s characterization of suffering as fear and grief experienced in response to a “threat to the integrity of the individual” reflects the disabling corporeal and psychological impact of chronic pain (21).

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According to Moskowitz, suffering is not an emotion but an “emotionally competent stimulus,” given that it is caused by an emotional state (pain and/or depression) and evokes other emotions (such as rage, disgust, etc.) to motivate palliative

actions. Thus, suffering (like chronic pain and depression) does not directly motivate corrective behavior, but rather, as Moskowitz notes, is “...involitional, resulting in withdrawal, stasis, and inaction.” By this portrayal, it is the stressful experience of suffering in conditions of chronic pain that entails the psychological, behavioral and social factors of the pain experience that contribute to resultant distress, depression, and disability. Furthermore, the concept of neurobiological suffering may directly address why depression is likely to result from chronic pain (and perhaps other chronic neurological conditions) (21). While suffering is usually described in somewhat metaphysical terms, a portrayal of the neural basis of suffering elucidates the substrates of a chronic pain-depression spectrum disorder that may contribute to and/or evoke suffering.

We have hypothesized that common genetic and environmental predispositions to chronic pain—which may include the combined effects of 1) particular neuropharmacologic genotypes and phenotypes, 2) nociceptive sensitivity, 3) social factors contributing to

the psychological development of negative schemas or learned helplessness, and 4) psychological and physiological responsivity to stress — might also predispose an individual to depression (23,4). Still, it is likely that no one single factor is universally causal, but rather that multi-factorial changes occur in molecular, chemical, structural elements of these neuraxes (i.e. a “bottom-up” effect). Through modification of in brain function and (micro and macro) structure to affect the systems’ properties of various neural networks, such changes thereby manifest “top-down” effect(s) in which the activities of altered brain function evoke changes in network properties of various neural systems (that mediate physiological effects, cognition, emotion and behavior(s) (22-24).

This prompts consideration of common pathological mechanism(s) that are related and involved in the co-morbid presentation of chronic pain and depression. We posit that an “essential” underlying factor is the disruption or loss of non-linear adaptive properties within and between particular brain networks, and the progressive linearity of aberrant functions that manifest effects from the cellular to the cognitive-behavioral levels (23,24). In our model, peripheral and/or central inflammatory processes contribute to, or directly elicit such change(s) by disrupting glial-neuronal regulation, altering neurochemistry, and inducing functional and/or structural abnormalities in neural networks (25).

Such questions of co-morbidity, correlation and/or causality also compel inquiry to examine how, why, and in whom the various expression(s) of spectrum disorders occur. We maintain that particular genotypic factors predispose endo- and exophenotypes that are differentially expressed through interaction(s) with internal and external environmental influences throughout the lifespan (21). The goals, therefore, are first to determine how this combination of genotype and environment determines the type and extent of pathologic phenotype(s) expressed in certain individuals and populations, and second, to identify those physiologic and environmental substrates that are viable targets for therapeutic interventions to mitigate the development and expression of pain spectrum disorder.

As a diagnostic framework, the spectrum schema could serve as a basis for improved types and scope(s) of care... and could yield personalized therapeutics that are directed at the underlying disorder, rather than simply attempting to manage symptoms.

Conclusion

The spectrum model that we described accounts for the neurobiological, and psychosocial features of co-morbid chronic pain and depression. The notion of a chronic pain-depression spectrum disorder may more accurately

reflect the complexity of this pathology, in which the neural (and perhaps environmental) factors that evoke and sustain chronic pain and depression dynamically interact to yield observable clinical dysfunction. As a diagnostic framework, the spectrum

schema could serve as a basis for improved types and scope(s) of care, in order to more effectively prevent sub-clinical components from surpassing an objective threshold, and could yield personalized therapeutics that are directed at the underlying disorder, rather than simply attempting to manage symptoms.



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