UNDERSTANDING THE CO-OCCURRENCE OF ANXIETY DISORDERS AND CHRONIC PAIN: STATE-OF-THE-ART

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The purpose of this article is to describe the current state-of-the-art regarding the co-occurrence of the anxiety disorders and chronic pain. First, we describe the core characteristics of chronic pain and its co-occurrence with the anxiety disorders. Second, we review data on the prevalence of co-occurrence. Third, we describe the mutual maintenance and shared vulnerability models, both of which have been offered to explain the co-occurrence of posttraumatic stress disorder (PTSD) and chronic pain and may have applicability to various other anxiety disorders. Fourth, we provide an integrative review of available research addressing the postulates of these models specific to the mechanisms of anxiety sensitivity, selective attention to threat, and reduced threshold for alarm. We conclude with general recommendations for improving assessment and treatment of patients who present with an anxiety disorder accompanied by clinically significant pain. Given that most of the available evidence has come from studies of PTSD and chronic pain, we provide a detailed agenda for future investigation of the co-occurrence of chronic pain and other anxiety disorders. Depression and Anxiety 26:888–901, 2009.

INTRODUCTION

A substantial literature supports clinically important associations between psychiatric illness and chronic medical conditions and, while much of the research to date has focused on depression, there is growing evidence that anxiety and its disorders can increase the risk of incident medical illness and related complications[1,2] and vice versa.[3] There has been a rapid growth in research over the past 15–20 years on the co-occurrence of chronic pain and anxiety and its disorders; this growth pattern mirrors but exceeds the pattern for research on co-occurrence of depression and chronic pain over the past 10 years (see Fig. 1). In this review, our goals are to describe the core characteristics of chronic pain and its co-occurrence with the anxiety disorders. To do so we will review data on the prevalence of co-occurrence, consider models that have been offered to explain the co-occurrence, and review available research addressing the postulates of these models. The focus of these models and much of the relevant research in this emerging area is on co-occurring chronic pain and posttraumatic stress disorder (PTSD). We highlight the implications these models and research have for understanding the co-occurrence of chronic pain with other anxiety disorders. We conclude with general recommendations for improving assessment and treatment of patients who present with an anxiety disorder accompanied by clinically significant pain, and we provide a detailed agenda that outlines areas in need of additional research.

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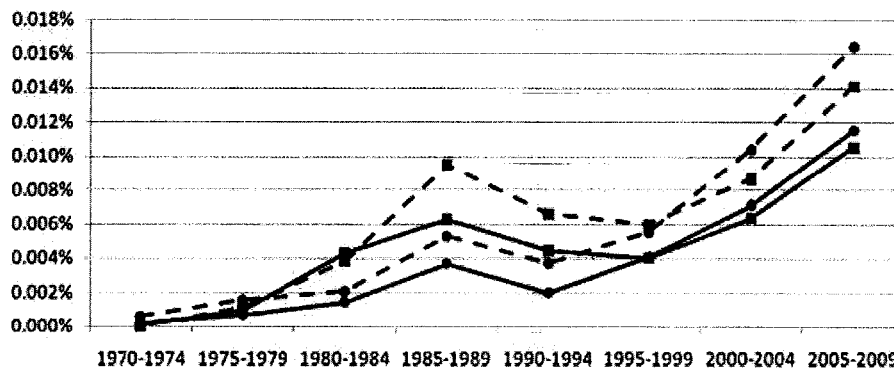
Figure 1. Graph representing percentage of Science Direct (solid line) and PubMed (dashed line) dealing with chronic pain and anxiety, fear, and anxiety disorders (circles) and chronic pain and depression (squares). Article counts were derived using the search engines provided by Science Direct and PubMed (Medline). Science Direct articles regarding Chronic Pain and Anxiety, Fear, or Anxiety Disorders were drawn from within each date range using search terms [i.e., "chronic pain" AND ("anxiety" OR "fear" OR "anxiety disorder" OR "obsessive–compulsive disorder" OR "posttraumatic stress disorder" OR "PTSD" OR "phobia" OR "panic disorder" OR "generalized anxiety disorder" OR "GAD" OR "social anxiety disorder" OR "social phobia")] placed in the "Abstract, Title, Keywords" search field. Science Direct articles regarding Chronic Pain and Depression were drawn from within each date range using search terms (i.e., "chronic pain" AND "depression") placed in the "Abstract, Title, Keywords" search field. Similarly, PubMed articles for were drawn using Mesh and standard search terms comparable or identical to those used with Science Direct.

UNDERSTANDING PAIN

Pain was once conceptualized strictly as a sensory experience resulting from stimulation of specific high threshold receptors (nociceptors), such as might occur at the time of physical injury or from progressive disease. The implicit assumption of this view was that the relationship between nociceptor activity and pain experience was invariant; that is, nociceptive input always produced pain. It is now understood that pain is more than sensation (nociception). Contemporary models recognize that pain is a complex perceptual experience determined by sensory as well as psychological and social influences.[4,5] Pain allows adaptation to our environment, alerting us to potential or actual tissue damage and motivating us into action to limit further injury and begin a process of recovery.[6] Those who are born without the capacity to experience pain (e.g., people with congenital analgesia, a rare autosomal recessive genetic disease) often die in childhood from the effects of undetected life threatening injuries or diseases that are usually signaled by pain.[7]

For most people, physical injury or disease is accompanied by pain, which typically abates with time as healing occurs. For some people the pain does not subside and, instead, becomes chronic (i.e., persists for 3 months or more[8]). When chronic, pain loses its adaptive qualities and, instead, causes considerable emotional distress and impairment of social and occupational functioning; for example, many people with chronic pain make frequent physician visits, undergo excessive medical evaluations, and miss work and other important activities.[9] Chronic pain is currently one of the most common and costly chronic health conditions in North America; approximately 10% of the general population report having experienced

chronic idiopathic (i.e., noncancer related) pain in the past 12 months[10] at a direct cost of about $100 billion annually[11] and twice that amount when one includes indirect costs due to absenteeism and lost productivity.[12] Although chronic pain is often associated with negative outcomes, it is important to note that some people with chronic pain cope effectively, and adapt in a manner that allows them to maintain their quality of life.

EPIDEMIOLOGY OF CO-OCCURRENCE

Most data on co-occurrence comes from examination of the prevalence of anxiety disorders in samples that report chronic pain. Data from the US National Comorbidity Survey Part II (NCS[13]) indicate that the prevalence of any DSM-III-R defined anxiety disorder in community dwellers with chronic arthritic pain at time of assessment is elevated relative to the general population (35 vs. 17%). These findings have been replicated and extended to patients with migraine and chronic back pain using data from the Midlife Development in the United States Survey[14] and, for DSM-IV defined anxiety disorders, the NCS Replication.[15] Findings from community-dwelling adults (n = 85,088) from 17 countries indicate that those with back or neck pain are two to three times more likely to have had past 12-month panic disorder (PD), agoraphobia, or social anxiety disorder (SAD), and almost three times more likely to have had generalized anxiety disorder (GAD) or PTSD.[16] Data on lifetime prevalence show similar patterns; specifically, community-dwelling women with fibromyalgia are four to five times more likely to have had a lifetime diagnosis of

obsessive–compulsive disorder (OCD), PTSD, or GAD than those without.[17]

In treatment-seeking samples, some[18,19] but not all[20–23] studies indicate elevated prevalence of any current anxiety disorder at time of assessment (25–29%) relative to the general population (18%[24]), as well as specific elevations in the prevalence of current SAD, GAD, PD, and PSTD. Caution is warranted in interpreting these findings given that the studies differ in the nature and size of samples, the methods used for assessing anxiety disorders, the DSM criteria employed, and the spectrum of anxiety disorders included in assessment (see Table 1). Similar cautions are warranted with respect to comparing findings from community samples (as described in the preceding paragraph) and treatment-seeking samples. Lifetime prevalence rates of any anxiety disorder have also been found to be elevated, relative to the general population (28%[25]) in some[18] but not all[19,23] studies of patients with chronic pain-seeking treatment.

A small but growing number of studies have assessed the prevalence of clinically significant pain conditions in people with anxiety disorders; however, this research has, for the most part, been limited to PD and PTSD. Kuch et al.[26] reported that 40% (54 of 141) of consecutively referred patients with PD reported chronic pain—most commonly in the head, shoulders, and lower back—and 10% were using analgesic medications on a daily basis. In a study of 71 patients with PD, Schmidt and Telch[27] identified a variety of comorbid physical conditions, including chronic back problems (46%), arthritis (22%), and other potentially painful conditions such as migraine, cancer, and diabetes (24%). Schmidt et al.[28] found that only

TABLE 1. Prevalence of anxiety disorders among treatment seeking chronic pain patients

Study	Participants	Diagnostic criteria	Prevalence at assessment (%)	
Reich et al. (1983)	Mixed chronic pain patients ($n = 43$)	DSM-III	Any anxiety disorder[a]	7.0
Katon et al. (1985)	Mixed chronic pain patients ($n = 37$)	DSM-III	Any anxiety disorder[b]	16.2
Large (1986)	Mixed chronic pain patients ($n = 50$)	DSM-III	Any anxiety disorder	8.0
			GAD	4.0
			PD	2.0
			PTSD	2.0
Fishbain et al. (1986)	Mixed chronic pain patients ($n = 283$)	DSM-III	Any anxiety disorder	19.4
			AG and/or SiP	2.1
			GAD	15.2
			OCD	1.1
			PTSD	1.1
Atkinson et al. (1991)	Chronic low back pain patients ($n = 97$)	DSM-III	Any anxiety disorder	28.8
			GAD	13.4
			PD	7.2
			OCD	8.2
Kinney et al. (1993)	Chronic back pain patients ($n = 90$)	DSM-III-R	Any anxiety disorder	25.0
			PD	3.0
			Phobic disorders[c]	13.0
			OCD	3.0
			PTSD	2.0
			GAD	4.0
Polatin et al. (1993)	Chronic low back pain patients ($n = 200$)	DSM-III-R	Any anxiety disorder	17.0
			PD	3.0
			Phobic disorders[c]	9.0
			OCD	2.0
			PTSD	1.0
			GAD	2.0
Asmundson et al. (1996)	Chronic musculoskeletal pain patients ($n = 200$)	DSM-IV	Any anxiety disorder	17.0
			PD	2.1
			SP	11.0
			SiP	2.7
			OCD	0.0
			PTSD	2.1
			GAD	0.0

Note: AG = Agoraphobia; PD = Panic Disorder; OCD = Obsessive-Compulsive Disorder; PTSD = Posttraumatic Stress Disorder; GAD = Generalized Anxiety Disorder; SP = Social Phobia (also called social anxiety disorder); SiP = Simple Phobia; Not all studies evaluated all anxiety disorders.
[a]all anxiety disorder cases diagnoses as PTSD.
[b]all anxiety disorder cases diagnosed as PD.
[c]nature of phobic disorder (i.e., social phobia, simple phobia, or both) not defined.

29% of a sample of 139 PD patients did not report current pain symptoms, with the remainder endorsing one or more of headache pain (55%), chest pain (34%), joint pain (25%), and stomach pain or ulcer (22%). These studies provide preliminary evidence that chronic pain, particularly of musculoskeletal origin, is more prevalent in patients seeking treatment for PD than the approximate 10% reported for the general population.[10,13] There is also preliminary data showing that patients with SAD do not differ from those with PD in prevalence, nature (i.e., primarily musculoskeletal), or experience (e.g., significant interference with daily activity) of chronic pain.[29]

People with PTSD report chronic pain with striking frequency; indeed, upwards of 30% of those seeking outpatient treatment for PTSD from community and mental health clinics, and 50–80% of military veterans and volunteer firefighters with PTSD, report chronic pain (for recent reviews, see[30,31]). These findings generalize across gender.[4] Sareen et al.[1] used data from the US NCS Part II to evaluate associations between the anxiety disorders and diagnoses of general medical conditions, including those for which pain is often a significant component. After controlling for socio-demographic variables and other common mental disorders (e.g., mood disorders, substance use disorders), robust associations were found between the physical disorders and each of PTSD, panic attacks, and agoraphobia. Of particular note, in addition to being twice as likely as others to have had one or more past-year physical disorders (e.g., neurological disorders, gastrointestinal disorders, metabolic or immune disorders) after adjusting for the other anxiety disorders, those with PTSD were 2.5 times more likely to have had a past-year bone or joint condition (e.g., arthritis, rheumatisms, other bone/joint disease).

These data suggest, with reasonable consistency, that chronic pain and the anxiety disorders—particularly PTSD, PD, GAD, and SAD—frequently co-occur. Whereas studies evaluating the prevalence of various anxiety disorders in people reporting chronic pain are common, there are fewer studies assessing chronic pain in people with anxiety disorders; thus, further investigation is warranted, beginning with replication of findings in community and treatment-seeking samples, using comprehensive pain assessment batteries.

Few studies have systematically investigated the temporal primacy of these conditions when they co-occur; determining the extent to which anxiety disorders precede the onset of pain, or vice versa, is one critical path to understanding the mechanisms that link the two conditions. The temporal relationship between the two may, in part, depend on the specific nature of the anxiety disorder. For example, the onset of PTSD and chronic pain may coincide temporally in the case of a person exposed to a traumatic stressor that involved a physical injury (e.g., whiplash injury following a motor vehicle accident). Whether this is the case for traumatic stressors not associated with personal physical injury (e.g., witnessing someone being injured) and for the other anxiety disorders remains to be determined.

There is preliminary evidence to suggest that, in some instances, anxiety disorders precede the onset of pain. Specifically, in a sample of injured workers with chronic musculoskeletal pain, the anxiety disorder predated the pain complaint in all but one case (i.e., panic symptoms and injury with close temporal onset).[20] It has also been found that among 90 chronic low back pain patients, 23% had a preexisting anxiety disorder.[19] Other evidence indicates that the probability of an anxiety disorder occurring before vs. after pain onset is similar. In a study of 97 chronic back pain patients, 30 of whom had a comorbid anxiety disorder, 46.7% reported onset of anxiety before pain, and 53.3% reported onset after pain.[18] In the only prospective study to date, we recently demonstrated that pain intensity and trauma-related emotional numbing, but not trauma-related avoidance, measured concurrent with disability made unique contributions to the prediction of 6- and 12-month postsurgical pain disability in pain patients undergoing postero-lateral thoracotomy.[32] The relative contribution of pain intensity decreased, whereas that of emotional numbing increased, with time, indicating a progressive de-coupling of pain intensity and disability and a concomitant strengthening of the link between emotional numbing and disability; thus, trauma-related emotional numbing may be important in the development and/or maintenance of pain disability.

Additional research is needed, particularly that which uses prospective methods, to delineate the temporal primacy of anxiety disorders and chronic pain when they co-occur and to determine factors that influence the transition from acute to chronic pain and disability. The findings that for some people the anxiety disorder and chronic pain develop coincidently, and for others that one condition predates the other (or vice versa), most likely speaks to the multiple mechanisms (reviewed below) that link various anxiety disorders and chronic pain.

MODELS

The substantial degree of co-occurrence of the anxiety disorders and clinically significant pain experiences suggests that these conditions are related in some way. Yet, establishing co-occurrence provides neither an understanding of the nature of the associations between the conditions nor an understanding of the mechanisms by which they are linked. As described elsewhere,[30] there are several possible scenarios that might explain the relationship. For any two conditions, possible relationship scenarios are as follows: (1) one causes the other (i.e., the anxiety disorder causes pain or vice versa), (2) they influence one another in some mutually maintaining way (e.g., pain exacerbates symptoms of the anxiety disorder and vice versa),

(3) some third factor (e.g., a common predisposition, a shared environmental event) increases vulnerability to both, or (4) they are independent, each being caused by mechanisms unrelated to the other. The second and third possibilities are not mutually exclusive; the fourth is not dealt with further here as there are no data to support this position and the co-occurrence rates refute it (i.e., if they were independent the rate of co-occurrence would be expected to equal the product of their separate probabilities).

There are, to the best of our knowledge, no theoretical positions that explicate the first of the possibilities noted above. Several models based on the second and third possibilities have been posited to explain the relationship between specific anxiety disorders and chronic pain. These models have been developed in the context of efforts to understand mechanisms underlying co-occurring PTSD and chronic musculoskeletal pain, and are based on tenets of empirically supported cognitive–behavioral models of anxiety and its disorders, PTSD,[33,34] and chronic musculoskeletal pain.[35–38]

The mutual maintenance model[39] (see Fig. 2) holds that physiological, affective, and behavioral components of PTSD maintain or exacerbate symptoms of pain and, similarly, that cognitive, affective, and behavioral components of chronic musculoskeletal pain maintain or exacerbate symptoms of PTSD. Seven specific mechanisms of mutual maintenance (see the central box in Fig. 2), each of which may have an impact along several pathways (see bi-directional arrows between central to outer boxes in Fig. 2) are posited in the model. The model predicts, for example, that pain sensations experienced by a person with chronic musculoskeletal pain will be persistent and arousal-provoking reminders of the trauma that precipitated the pain. Physiological arousal in response to recollection of the trauma will, in turn, promote

avoidance of pain-related activities and (over time) physical deconditioning, which makes the experience of pain more likely. The person thereby becomes trapped in a vicious cycle whereby the symptoms of PTSD and chronic musculoskeletal pain interact to produce self-perpetuating distress and functional disability.

Asmundson et al.[30,40] and others[31,41] have extended the mutual maintenance model, suggesting that some maintenance factors denote a shared vulnerability, or diathesis, for developing both conditions. The shared vulnerability model (see Fig. 3) posits that individual difference factors (Psychological Vulnerability box in Fig. 3), possibly genetically influenced, predispose people to develop PTSD and chronic musculoskeletal pain when exposed to certain environmental conditions (Life Event box in Fig. 3). Specifically, the model suggests that the interaction of a psychological vulnerability for feelings of loss of control (and anxiety), a lowered physiological threshold for alarm reactions (i.e., activation of physiological processes that prepare one to fight, flee, or freeze; Low Threshold for Alarm box in Fig. 3) to stressors, and instigating stressful events (e.g., traumatic incident, injury) all influence negative emotional responses (Emotional Response box in Fig. 3), their consequences (i.e., physiological, behavioral, and cognitive effects), and explain the development of PTSD, chronic musculoskeletal pain, and their co-occurrence (Disabling Condition box in Fig. 3). Co-occurring PTSD and chronic musculoskeletal pain are most likely to develop in cases where vulnerable people are exposed to an event that is both traumatic and painful, wherein reminders of the trauma and sensations of pain can serve as triggers for further alarm reactions. The latter is consistent with postulates of the mutual maintenance model and further illustrates how predisposing factors can contribute to maintenance of these conditions.

Our understanding of co-occurring PTSD and chronic musculoskeletal pain might apply to other anxiety disorders that frequently co-occur with chronic pain. Symptoms of physiological arousal and lack of positive emotions—both general characteristics of the anxiety disorders—may maintain or exacerbate symptoms of pain. Likewise, one or more aspects of the pain experience (e.g., physiological arousal, pain-related catastrophizing, avoidance of physical exertion) may maintain or exacerbate clinically significant symptoms of anxiety. Asmundson et al.[42] have suggested that symptoms of anxiety and pain may interact to promote clinically significant distress or impairment in persons with other anxiety disorders. This notion is primarily predicated on findings from the investigation of co-occurring PTSD and chronic pain as well as several studies of pain experiences in patients with PD (as discussed below). However, studies of co-occurring PTSD and chronic pain are potentially confounded because a traumatic event involving personal physical injury (e.g., road traffic accident, work-related or combat injury, physical assault) often precipitates both
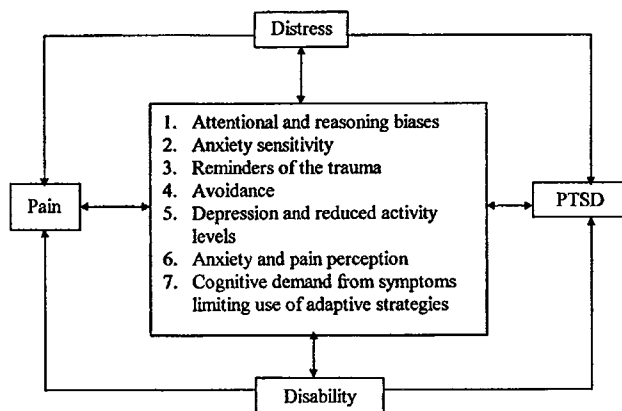

Figure 2. Mutual maintenance model. From Sharp TJ, Harvey AG: Chronic pain and posttraumatic stress disorder: mutual maintenance? Clinical Psychology Review 2001;21(6):857–77, p. 870. Copyright 2001. Reprinted with permission from Elsevier Science.
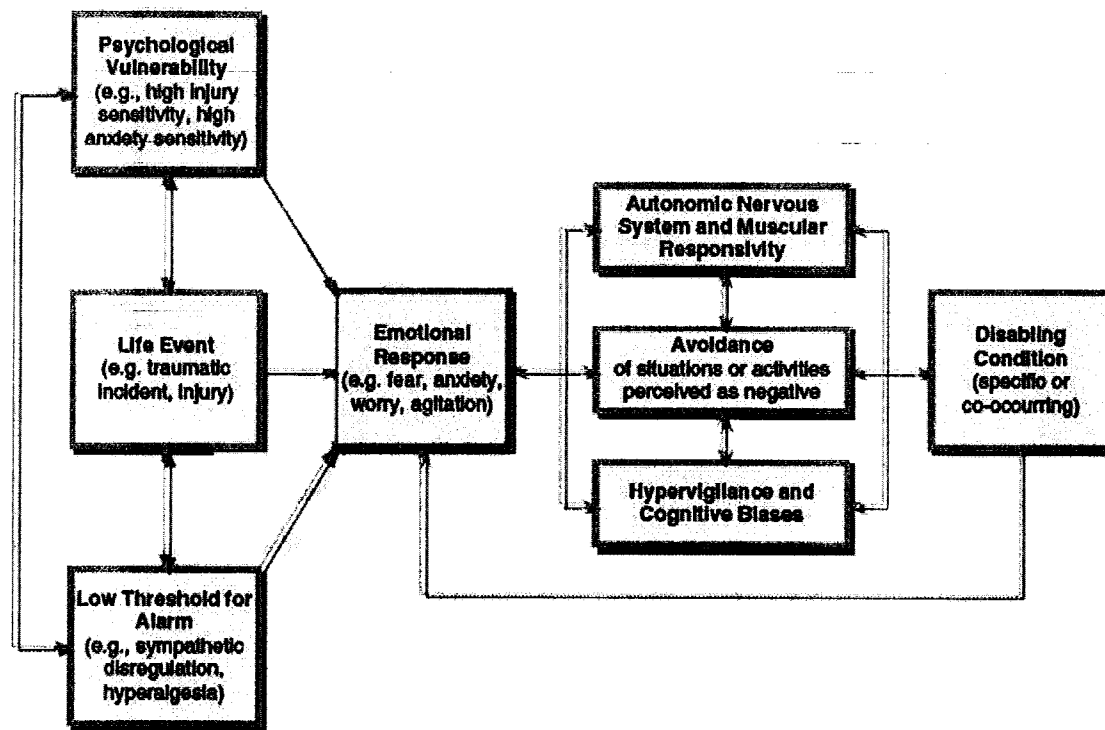
Figure 3. Shared vulnerability model. From Asmundson GJG, Abrams MP, Collimore KC: Pain and anxiety disorders, in Health behaviors and physical illness in anxiety and its disorders: Contemporary theory and research. Edited by Zvolensky MJ, Smits JAJ. New York: Springer, 2008, pp 207–235, p. 216. Copyright 2008. Reprinted with permission from Springer Science and Business Media.

pain and posttrauma emotional reactions. A fruitful avenue for future studies of this model, and the mechanisms underlying co-occurrence of the anxiety disorders and chronic pain, may be to focus on other anxiety disorders, such as PD, wherein the onset of symptoms of each conditions are not often associated with a shared experience.

REVIEW OF EMPIRICAL SUPPORT

As noted above, evidence supporting the postulates of the mutual maintenance and shared vulnerability models has been garnered primarily in the context of studies of co-occurring PTSD and chronic musculo-skeletal pain. There is considerable symptom overlap between PTSD and chronic musculoskeletal pain. Both are characterized by somatic hypervigilance and (possibly) biases in attention toward threatening stimuli, heightened startle reaction, emotional numb-ing (e.g., absence of positive emotion), avoidance, and dysregulation in stress response and pain modulation systems.[30] These findings indicate that PTSD and chronic musculoskeletal pain share similar response patterns in the cognitive, behavioral, and physiological domains. There is also evidence to suggest that particular PTSD symptom clusters are more closely associated with certain aspects of the pain experience; for example, re-experiencing symptoms are uniquely

associated with pain severity, self-report of physical symptoms, and limitations in functional ability,[4,43,44] numbing is negatively related to role functioning at low levels pain,[45] and hyperarousal is associated with detection of pain.[46] Studies to date have identified anxiety sensitivity (AS), selective attention for threat, and lowered threshold for alarm as potential mechan-isms of co-occurrence.

AS AND OTHER POTENTIAL VULNERABI-LITY FACTORS

AS—fear of anxiety based on the belief that it may have harmful consequences—is an individual difference variable known to increase sense of danger and fearful responding. AS is elevated in patients with PTSD,[47,48] as well as most other anxiety disorders,[49] and in some patients with chronic musculoskeletal pain.[50] AS is positively correlated with the severity of PTSD symptoms,[51] severity of labor[52] and dental[53] pain, increases the risk of pain-related avoidance and disability following physical injury in adults[54] and in children with chronic pain,[55,56] and is partly influ-enced by learning[57] and genetic factors.[58] AS has been suggested to potentiate pain sensations in some patients with PD; indeed, although one study has reported that patients with PD had normal sensitivity to pain when compared to healthy control partici-pants,[59] another has shown that diagnostic status

(i.e., PD vs. healthy control) and AS are predictive of pain response to cold pressor.[60] AS has also been postulated to be responsible for the extreme emotional responses to trauma and pain associated with injury, and as a specific vulnerability factor that predisposes people to develop both PTSD and chronic musculoskeletal pain.[30,40,41] It has yet to be established that elevated AS precedes the development of PTSD and chronic musculoskeletal pain; thus, it remains a possibility that AS becomes elevated as a consequence of PTSD and chronic musculoskeletal pain and thereafter serves to maintain symptoms.[39] Longitudinal studies, in PTSD and across the spectrum of anxiety disorders co-occurring with chronic pain, are needed to assess these possibilities.

Additional study of other potential vulnerability factors (i.e., trait negative affectivity, illness/injury sensitivity, fear of negative evaluation, fear of pain, pain-related anxiety, alexithymia, discomfort intolerance) is also warranted, as there is emerging evidence that these play significant roles unique from AS in at least some of the anxiety disorders[61] and possibly chronic musculoskeletal pain.[62] For example, levels of pain-related anxiety in individuals with anxiety disorders have recently been reported as being comparable to levels reported by patients with chronic pain and higher than levels reported by community dwellers, suggesting that pain-related anxiety may warrant specific consideration for inclusion in anxiety disorder assessment and treatment.[63]

SELECTIVE ATTENTION TO THREAT

There is a considerable body of evidence indicating that people with various forms of psychopathology and general medical conditions selectively attend to threat-related stimuli representative of the core concerns of their specific disorder; that is, they direct attention toward objects or situations that they fear. This increases state anxiety and has potential to make one vulnerable for emotional disorders.[64,65] Evidence for syndrome-specific attentional biases is, with few exceptions, robust across the anxiety disorders.[65] Syndrome-specific attentional biases have been consistently demonstrated in patients with PTSD using emotional Stroop colour-naming and fear-potentiated startle tasks[66] but not with the dot-probe task.[67]

Findings are less robust for chronic pain. A meta-analytic review of five investigations using the emotional Stroop task suggests that chronic pain patients, compared to healthy participants, have an attentional bias to both sensory (e.g., "stabbing") and affective (e.g., "exhausting") pain words.[68] However, scrutiny of the findings from the individual investigations used in the meta-analysis, findings from more recent Stroop investigations,[69] results of some[70–73] but not all[74] dot-probe investigations, and results of some[75] but not all[76,77] investigations employing startle potentiated by pain-related and other stimuli, fail to provide

convincing evidence for this conclusion. The findings to date are equivocal.

An underlying assumption of attentional bias research in patients with chronic pain is that these patients are generally fearful of pain, view it as a threat, and, thus, selectively direct attention to pain-related stimuli. This assumption may be incorrect; indeed, it has been suggested that investigators have not identified the specific objects or situations that are feared by these individuals.[78] Pain-related stimuli may not be the only object of fear for many patients with chronic pain; several studies provide evidence that trauma-related stimuli may be the most relevant object of fear. When the heterogeneous nature of chronic musculoskeletal pain is considered, those patients classified as dysfunctional (e.g., greater pain severity, emotional distress, and activity limitations) are far more likely to have co-occurring PTSD (~70%) than those classified as interpersonally distressed (~35%) or as adaptive copers (~20%).[79] The robustness of findings from the attentional bias research in patients with PTSD implies that pain patients classified as dysfunctional selectively attend to trauma-relevant stimuli. Preliminary evidence supports this hypothesis; specifically, patients with co-occurring PTSD and pain show attentional biases for both pain and accident words (e.g., "crash") on the emotional Stroop task, whereas those with pain and no PTSD are biased only toward pain words (e.g., "throbbing").[80]

With regard to PTSD, these findings suggest that the object of fear in some chronic pain patients (i.e., those classified as dysfunctional) may be associated with prior traumatic and painful injury. Confirmation of these findings may explain the lack of robustness observed in efforts to identify attentional biases in patients with chronic pain and may shed light on cognitive mechanisms underlying the co-occurrence of these conditions. Extension to other anxiety disorders experienced in the context of chronic pain is also warranted.

LOWER THRESHOLD FOR ALARM

Pain and anxiety are both associated with physiological arousal (e.g., accelerated heart rate, elevated blood pressure, increased respiration rate, decreased gastrointestinal activity, increased muscular tension, increased blood flow to skeletal muscle).[81] The bodily changes stemming from arousal serve a protective function, promoting escape and withdrawal, but can have detrimental effects if prolonged. Physical injury and traumatic experiences also initiate other complex neural and hormonal processes (e.g., release of cytokines, β-endorphin, 5-HT-moduline) that, while designed to promote tissue healing and reinstate homeostasis, can be destructive to muscle, bone, and neural tissue when prolonged.[5,82] In short, prolonged physiological arousal and activation of neural and hormonal processes associated with the stress response,

whether initiated by pain or anxiety, act as stressors (i.e., they contribute to perceptions of threat and uncontrollability) that can have detrimental effects on various body systems.[83] Consistent with this view, strong associations have been reported between anxiety disorders, particularly PTSD, and general medical conditions characterized by pain.[1]

Chronic autonomic nervous system (ANS) arousal may be, at least in part, responsible for the symptoms of both PTSD and chronic idiopathic pain. One of the most robust findings in the PTSD literature is that sympathetic activity is increased and parasympathetic activity decreased, both in general and in response to trauma-related stimuli. This pattern of findings has been observed across a wide variety of measures of cardiovascular reactivity in both traumatized adults[84] and children.[85] Although ANS dysregulation in chronic musculoskeletal pain has received little empirical scrutiny, available findings suggest a pattern similar to that observed in PTSD. Rainville et al.[86] used hypnosis to alter mood, perceived pain unpleasantness, and severity of pain induced in healthy participants, showing that increases in negative mood and pain unpleasantness were positively associated with changes in heart rate variability. This suggests that pain-related emotion impacts ANS responsivity.

The literature regarding pain threshold (i.e., the point at which a stimulus is reported as being painful) and pain tolerance threshold (i.e., the length of time that a pain stimulus can be tolerated) in each of PTSD and chronic musculoskeletal pain may also provide some clues as to the mechanism of association; however, the findings are mixed and complex. There is, for example, a body of evidence indicating that hyperalgesia (i.e., reduced pain and tolerance thresholds indicating heightened pain perception) is induced by elevations in state and trait anxiety.[87,88] As elevations in state and trait anxiety are central features of PTSD and chronic pain, it is plausible that PTSD and chronic pain may induce hyperalgesia. On the other hand, there is a body of literature indicating that conditioned stress-induced hypoalgesia/analgesia (i.e., increased pain and tolerance thresholds indicating attenuated pain perception) plays an important and potentially causal role in both chronic musculoskeletal pain[89,90] and PTSD.[90] This literature suggests that dysregulation of the endogenous opioid system—perhaps functioning to deactivate fear structures (e.g., amygdala, hippocampus, thalamus) in the short term through heightened release of endogenous opioids—may play a role in blunting pain perception (e.g., higher pain threshold and tolerance), reducing avoidance behavior, and increasing emotional numbing associated with chronic pain and PTSD. Geuze et al.[91] reported that veterans with PTSD and no chronic pain, compared to veterans without PTSD, exhibited decreased sensitivity to fixed intensity heat pain stimuli as well as increased activation of the left hippocampus and decreased activation in the prefrontal cortex and right amygdala. More recently, Defrin[92] reported that that patients with PTSD (most of whom had chronic pain), but not clinical controls with an anxiety disorder other than PTSD or healthy controls, demonstrated hyposensitivity to non-noxious stimuli, hypoalgesia to at-pain threshold noxious stimuli, and hyperalgesia to stimuli above the threshold for pain. As we suggest elsewhere,[93] further investigations of the unique contributions to the perception of pain from PTSD symptoms and current (and chronic) pain experiences is warranted. This might entail, for example, investigating the relationship between pain perception and traumatic experiences that involve personal injury (reported by 50% of PTSD participants in the Defrin et al.[92] investigation) vs. those involving witnessing a traumatic event (without personal injury).

These mixed findings are even more intriguing when placed in the context of evidence showing that AS does not impact pain tolerance or threshold, but is associated with pain intensity.[54] It is possible that separate mechanisms are operating at different levels of the stimulus–response range (i.e., from just noticeable sensation through intolerable pain) and that these mechanisms are partially regulated by individual difference factors that direct the processing of pain sensations through brain structures that interpret the signal as alarming. Given that unpredictable and predictable pain are associated with hyperalgesia and hypoalgesia/analgesia, respectively,[94] it is equally possible that different mechanisms are activated depending on whether pain evokes anxiety (i.e., response to unpredictable, future threats) or fear (i.e., response to an immediate threat). Further investigation of these issues is also needed to clarify the state-of-the-art.

Chronic dysregulation of the ANS and endogenous opioid system appears to play important, possibly interactive roles in reducing the threshold for alarm in PTSD and chronic pain; as such, it may account for their co-occurrence. This remains to be evaluated in direct comparisons between those with PTSD, chronic pain, both PTSD and chronic pain, and healthy as well as clinical control participants. Combined with evidence that the serotonergic system may be dysregulated in both PTSD and chronic musculoskeletal pain,[95] this line of research may provide clues as to the peripheral and central physiological mechanisms underlying the suggestion of a lower threshold for alarm. As noted above in the context of research on cognitive mechanisms, extension of this research to other anxiety disorders experienced in the context of chronic pain is warranted.

SUMMARY

An obvious limitation of this review of empirical findings reflects a shortcoming in the current literature in that much of the research involving the mutual maintenance and shared vulnerability models focuses

on co-occurring PTSD and chronic pain. Few studies have systematically evaluated other anxiety disorders and their association with chronic pain experience. Empirical scrutiny of co-occurring anxiety disorders and chronic pain is in its infancy and, as is often the case in emerging fields of inquiry, there are more questions than answers. Notwithstanding these limitations, the mutual maintenance and shared vulnerability models provide a framework to guide future research as well as recommendations for assessment and treatment of individuals with a co-occurring anxiety disorder and chronic pain.

CLINICAL IMPLICATIONS

Clinically significant pain often goes unnoticed when assessing and planning treatment for a patient with an anxiety disorder. When overlooked, pain can make treatment of the anxiety symptoms complicated, frustrating, and ineffective; indeed, a recent secondary analysis of data from a randomized controlled trial of physician care as usual vs. collaborative care for PD or GAD indicated that pain severe enough to interfere with activities of daily living significantly reduced response to anxiety treatment.[96] Detailed assessment and treatment planning for patients with an anxiety disorder who present with co-occurring pain symptoms are presented elsewhere.[97] In general, comprehensive assessment of pain requires delineation of pain severity or intensity, pain location and distribution, attitudes and beliefs about pain and its effects, ways of coping with pain, pain-specific emotional distress (i.e., fear, anxiety, mood changes), and pain-related functional abilities and limitations.[98,99]

Cognitive–behavioural therapy (CBT) is highly effective for both anxiety disorders[100] and chronic pain;[101] therefore, treatment of clinically significant pain in patients with an anxiety disorder may effectively incorporate elements of CBT for both the anxiety disorder and chronic pain. Although there is very little research on treatment issues pertinent to co-occurrence, there are several treatment options that appear promising. Because exercise can serve the dual purpose of physical reconditioning in patients with chronic pain[102] and amelioration of anxiety symptoms, particularly panic-related symptoms,[103,104] it is an attractive consideration for the patient with both clinically significant anxiety and chronic pain symptoms. Exposure to specific pain-related activities that are feared or avoided (i.e., graded in vivo exposure)—one of the most effective techniques for reducing pain-related disability[105]—may prove effective in situations where a patient with an anxiety disorder reports significant fear and avoidance of pain-related situations or activities. Likewise, interoceptive exposure (i.e., exposure to anxiety-provoking bodily sensations), a frequent component of treatment for various anxiety disorders,[106] has recently been shown effective in reducing both PTSD symptoms[107] and fear of pain;[108] consequently, it may have significant potential as treatment for patients who present with a co-occurring anxiety disorder and chronic musculoskeletal pain. Acceptance and mindfulness-based interventions[109,110] have also been found to be effective for a range of medical and psychological problems that include pain syndromes and anxiety disorders.[111–113] It is plausible that these interventions may prove effective, either on their own or as adjuncts to CBT, for the treatment of anxiety disorders that co-occur with chronic pain.

Pharmacotherapy can be effective in alleviating pain associated with various conditions;[114] thus, combining analgesics with CBT may prove particularly effective in cases where an anxiety disorder and clinically significant pain co-occur. Combined pharmacotherapy and CBT is, in fact, recommended in current expert consensus guidelines for comorbid PTSD and chronic pain.[115] Interestingly, a growing body of evidence suggests that propranolol, a beta-blocker with analgesic effects, reduces PTSD symptoms[116–118] and erases fear conditioning;[119] gabapentin, a gamma-aminobutyric acid analogue, and anti-convulsant medication, is effective for alleviating headache[120] and musculoskeletal pain[114] as well as various anxiety disorders, including PD, PTSD, SAD, and GAD;[121–123] and, most recently, cortisol has been shown to impair memory of emotionally laden material, including pain words, but not neutral material.[124]

In contrast to the well-documented efficacy of SSRIs in management of the anxiety disorders, the literature is fairly consistent in failing to demonstrate significant improvement for patients with chronic pain conditions. Recent systematic reviews and meta-analyses indicate limited evidence for the benefits of SSRIs in patients with chronic low back pain,[125] migraine and tension type headaches,[126] and neuropathic pain;[127] however, we are unaware of any studies that have specifically examined the efficacy of SSRIs for co-occurring chronic pain and anxiety. Recent evidence indicates that paroxetine reduces anxiety-related behavior as well as thermal hyperalgesia and tactile allodynia in a rat model of neuropathic pain through its action at separate brain regions.[128] Future research is required to establish the specific value of these treatment options in the context of chronic pain that occurs across the various anxiety disorders.

AGENDA FOR FUTURE RESEARCH

Relatively little is known about the mechanisms that underlie the co-occurrence of the anxiety disorders and conditions characterized by clinically significant pain and, as noted above, the majority of evidence comes from investigations of the co-occurrence of PTSD and chronic musculoskeletal pain. Future research is needed to identify mechanisms responsible for

co-occurrence of chronic pain and the other anxiety disorders—PD, SAD, GAD, and OCD. Systematic inquiry may also allow further development, refinement, and empirical validation of treatments geared specifically toward those patients who have both an anxiety disorder and chronic pain.

Below we highlight a number of specific research directions that await investigation. Our list is necessarily cursory, but reflects a variety of research themes that may serve to advance the field. Many of these recommendations are in line with prior suggestions for advancing our understanding of the role of psychological factors in chronic pain.[129] For those investigators who pursue one or more of these directions, we urge careful attention to the heterogeneous nature of chronic pain (e.g., as illustrated by the Multiaxial Assessment of Pain categories of minimizers/adaptive copers, interpersonally distressed, dysfunctional[130]), as failure to do so may significantly reduce power to detect mechanisms at play. We also urge that efforts are made to evaluate aspects of both mental and physical health, to consider the role of the anxiety disorders in the transition from acute to chronic pain, and to be mindful of the influence of patient differences on treatment outcomes and the potential utility of treatment tailoring.

Further elaboration of current and lifetime prevalence of various pain conditions in each of the anxiety disorders, in community and treatment-seeking samples, using comprehensive pain assessment batteries is warranted. Of particular importance, investigation of the temporal primacy of co-occurring anxiety disorders and chronic pain is required to determine whether one condition is more likely to precede the other, whether sequencing of onset is consistent across the anxiety disorders, and what processes contribute to the transition from acute to chronic pain and disability in the context of co-occurrence. The latter will necessitate large-scale longitudinal studies that include comprehensive assessment of chronic pain and the anxiety disorders. Although it is beyond the scope of this review to delineate specifics of studies exploring anxiety constructs and/or processes and pain in children and adolescents, either with a pain-related condition[55,56,131] or undergoing acute laboratory pain procedures,[132] younger populations may prove well suited to further investigation of the temporal relationships between acute and chronic pain and the anxiety disorders.

Further empirical exploration of the mechanisms of co-occurrence, as posited in the mutual maintenance and shared vulnerability models, for various chronic pain conditions and each of the anxiety disorders will improve our understanding of co-occurrence. It will also permit model refinement. Given the number of mutual maintenance and shared vulnerability mechanisms that may be operating in the context of various co-occurring chronic pain conditions and anxiety disorders, this is an area with many research directions.

Initial work guided by successes in delineating the mechanisms of co-occurring chronic pain and PTSD may serve to significantly advance our understanding of the co-occurrence of chronic pain and the other anxiety disorders.

The following studies of potential mechanisms are required to advance the field: (a) longitudinal studies to examine whether elevated AS precedes the development of anxiety disorders and chronic musculoskeletal pain, or whether it becomes elevated as a consequence of these conditions; (b) study of other potential vulnerability factors (i.e., trait negative affectivity, illness/injury sensitivity, fear of negative evaluation, fear of pain, pain-related anxiety, alexithymia) to likewise determine their role in the development and maintenance of co-occurrence of chronic pain with each of the anxiety disorders; (c) further examination of the object of fear in chronic pain patients with and without a co-occurring anxiety disorder other than PTSD; and (d) examination of the possible interactive roles of ANS dysregulation and the endogenous opioid system in reducing threshold for alarm and altering pain perception and processing in PTSD alone, each of the other anxiety disorders alone, and in the co-occurrence of each of these anxiety disorders with chronic pain. In this latter context, specific consideration of discomfort intolerance (i.e., an inability to tolerate uncomfortable sensations)[60] and the potential vulnerability factors described above may prove particularly fruitful.

The preliminary research regarding the application of various pharmacologic agents with anxiolytic and analgesic properties, as well as interoceptive exposure, in this context is promising; yet, additional treatment research is also needed. Issues of treatment sequencing (e.g., treating the chronic pain first, the anxiety disorder first, or both concurrently), treatment preferences, treatment tailoring, and other factors that improve treatment outcome for co-occurring chronic pain and anxiety disorders is required to successfully guide treatment. In this regard, and also potentially important to the issue of mechanisms, establishing the extent to which the anxiety disorders and chronic pain share common emotion-generative processes (i.e., evaluation of internal and external emotional cues) and ineffective strategies for emotion regulation (e.g., suppression of emotion[133,134]), may serve to guide treatment and improve treatment outcomes. Empirical scrutiny of prevention and other early intervention strategies for those with anxiety disorders accompanied by clinically significant pain may also prove fruitful in reducing transition from acute to chronic pain and the degree of disability.

The suggestions above by no means represent a comprehensive research agenda. Rather, we offer these suggestions as potential starting points for facilitating discovery of evidence that will improve our understanding of the co-occurrence of anxiety disorders and chronic pain. The current state-of-the art is informed

primarily by studies of co-occurring PTSD and chronic pain and a handful of studies that have considered pain experiences in other anxiety disorders. It is our hope that this review will stimulate further exploration within the context of each of the anxiety disorders and, ultimately, lead to preventive and intervention strategies that reduce suffering and disability associated with co-occurring anxiety and chronic pain.

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