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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Contract grant sponsors: Canadian Institutes of Health Research (CIHR); Institute of Neurosciences Mental Health and Addiction.

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Received for publication 22 April 2009; Revised 6 July 2009; Accepted 8 July 2009

DOI 10.1002/da.20600
Published online 18 August 2009 in Wiley InterScience (www.interscience.wiley.com).

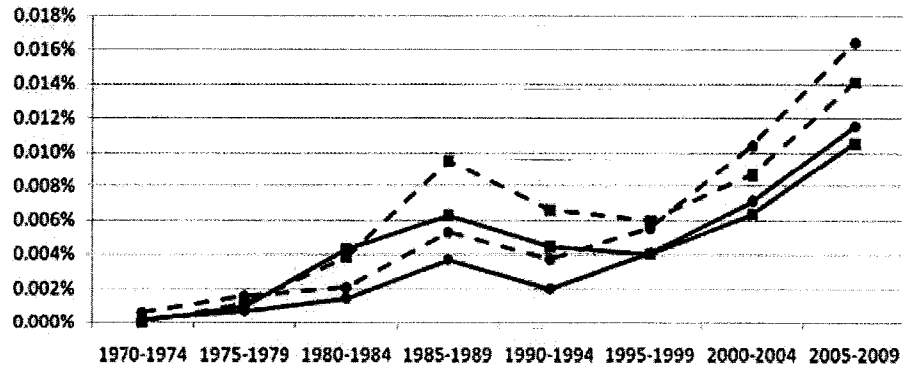

Figure 1. Graph representing percentage of Science Direct (solid line) and PubMed (dashed line) dealing with chronic pain and anxiety, fear, and anxiety disorders (circles) and chronic pain and depression (squares). Article counts were derived using the search engines provided by Science Direct and PubMed (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

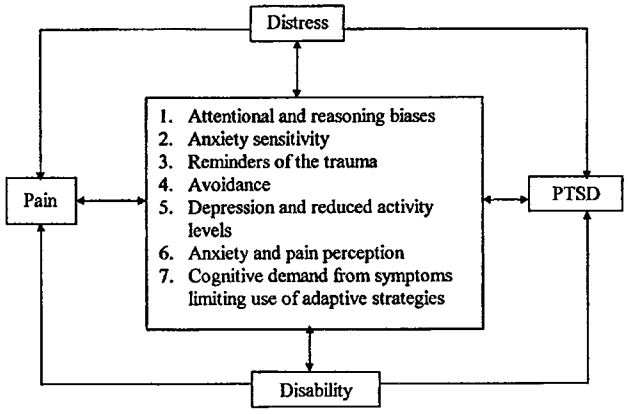

Figure 2. Mutual maintenance model. From Sharp TJ, Harvey AG: Chronic pain and posttraumatic stress disorder: mutual maintenance? Clinical Psychology Review 2001;21(6):857–77, p. 870. Copyright 2001. Reprinted with permission from Elsevier Science.

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

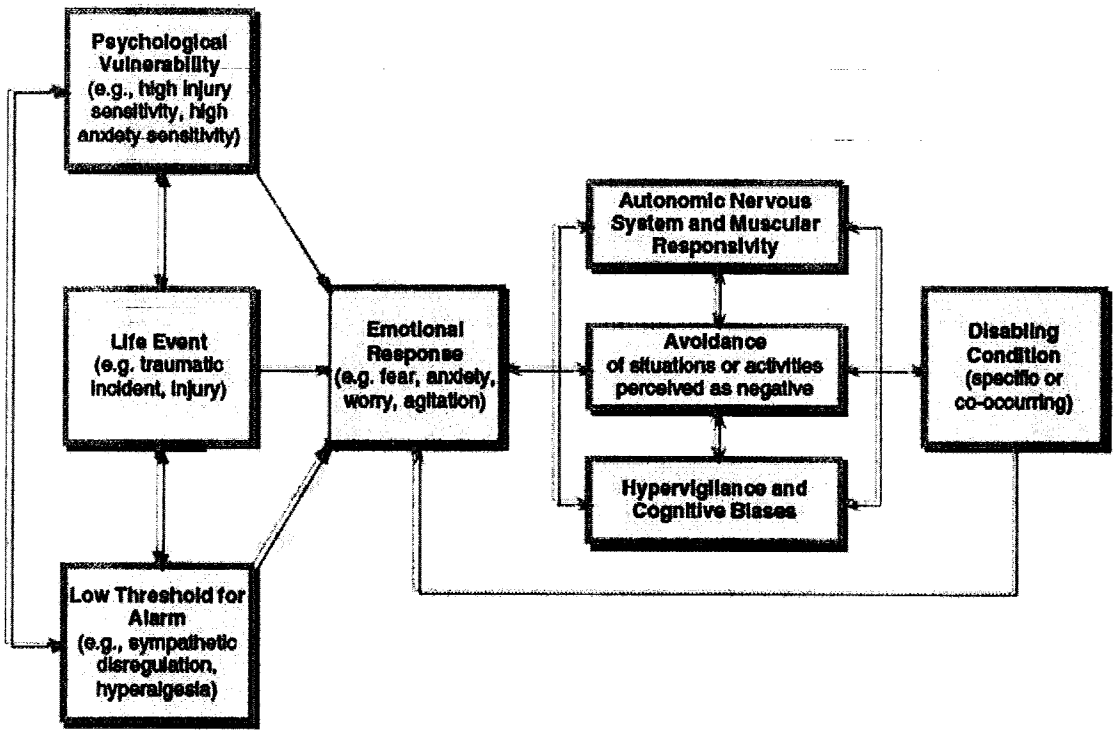

Figure 3. Shared vulnerability model. From Asmundson GJG, Abrams MP, Collimore KC: Pain and anxiety disorders, in Health behaviors and physical illness in anxiety and its disorders: Contemporary theory and research. Edited by Zvolensky MJ, Smits JAJ. New York: Springer, 2008, pp 207–235, p. 216. Copyright 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 musculoskeletal 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 numbing (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 mechanisms of co-occurrence.

AS AND OTHER POTENTIAL VULNERABILITY 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 influenced 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 participants,[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