Anxiety and Pain

No Grand Inquisitor has in readiness such terrible tortures as has anxiety, and no spy knows how to attack more artfully the man he pursues, choosing the instant when he is weakest, nor knows how to lay traps where he will be caught and ensnared, as anxiety knows how. – Søren Kierkegaard

Chronic dysfunction of bodily alarms transforms adaptive symptoms into disease states.

Anxiety, like pain and fear, plays an adaptive role as an alarm that responds to danger or harm. Chronic dysfunction of these alarms transforms an adaptive symptom into a disease state. Since these alarms serve similar protective functions, it is predictable that they might interact and also elicit collective effects. For example, interventions that lessen anxiety may dramatically reduce pain in an individual whose pain is amplified by anxiety. Likewise, analgesia may lessen anxiety that is amplified by pain. In such cases it would be an oversimplification to conclude that pain is not genuine or that somatic sensations are not worthy of further attention or treatment. This issue of Pain: Clinical Updates surveys the intricate psychological and biological interplay of these distinct alarm systems.

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History

Anxiety and pain have been documented since the beginning of recorded history and are believed to be experienced by most, if not all, humans and animals. Early interpretations of anxiety disorders in classical Greece were spiritual. The word “panic” is derived from the Greek god Pan, who, according to legend, could inspire overwhelming and irrational fear, especially when one was disturbed from sleep. The term anxiety comes from the Latin “angere,” meaning to choke or strangle, appropriately depicting typical features of what we today think of as anxiety symptoms. Ancient Russian tribes recognized feelings of panic and anxiety and were known to use mind-altering drugs to reduce fear and pain to enhance the prowess of their warriors. The linking of pain, anxiety, and the affective quality of pain derives from Aristotle, who described pain as “outside the senses and within the passions of the soul.” In the 16th century, most cases of anxiety were labeled as “hysteria,” a term derived from the Greek word for uterus. It was believed that anxiety predominantly affected women of childbearing years, caused by a “wandering uterus.” During the late 19th century, Freud popularized the term “anxiety neurosis,” which played a central role in his theories of psychopathology. He theorized that much hysteria and anxiety could be explained through analysis of patients’ childhood and adult sexual experiences.
In 1896, Von Frey explicitly recognized affect within the pain experience but considered it to be merely a secondary, reactive component. Melzack and Casey later documented an affective-motivational dimension of pain that contributes to overall pain intensity. Although the notion of persistent pathological anxiety has been a central concept in psychiatry since the founding of the discipline in the 19th century, the American Psychiatric Association did not introduce the diagnosis of generalized anxiety disorder in its Diagnostic and Statistical Manual of Mental Disorders until its third edition (DSM-III) in 1980. Previously, these disorders were given generic descriptors such as “stress” or “nerves.” Today the association between emotional distress and physical symptoms is formally recognized by the American Psychiatric Association.

Anxiety Versus Fear

Anxiety is an emotional state that we all experience to some degree. Classic symptoms include rapid heartbeat, nervousness, muscle tension, sweating, nausea, dizziness, headache, and insomnia. Mild to moderate anxiety is normal in certain situations and may even be beneficial, possibly motivating an individual to prepare for a performance, eliciting vigilance during a challenging task, or serving as a warning of danger. Problems arise when a person experiences too little or too much anxiety. Anxiety disorders are distinguished from “normal anxiety” by their intensity, prolongation, or association with phobias that interfere with function. Anxiety symptoms are typically assessed in three domains: cognitive or affective (e.g., fearfulness, nervousness, uneasiness, irritability, and tenseness); behavioral (e.g., immobility, avoidance, restlessness, nonfluent speech, and hyperventilation); and physiological (e.g., increased blood pressure, shortness of breath, nausea, sweating, and faintness). Diagnostic criteria for specific anxiety disorders have been classified by the American Psychiatric Association.

Although fear and anxiety both involve intense, unpleasant feelings of dread, fear differs from anxiety in that the source of fear is typically an identified threat. The event that one fears is usually within the bounds of possibility. While fear is usually a response to an external stimulus, anxiety is an internal process. Dysfunctional anxiety occurs when an individual cannot specify the object of dread, or when feelings of dread are not closely associated with an identified danger or threat. Anxiety is a disproportionate response to a vague, distant, or even unrecognized danger. For example, one may be anxious about “losing control” during a painful situation or experience.

Prevalence and Comorbidity

It is estimated that about one in every five or six persons suffers from chronic pain. There is increasing evidence that psychological disorders such as depression or anxiety often coexist with chronic pain and may be correlated with chronic pain. One study found that 35% of the population with chronic pain met criteria for an anxiety disorder compared with only 18% of the general population. DSM-IV criteria for a concurrent anxiety disorder was met in 26 of 146 disabled workers with chronic musculoskeletal pain. Varni et al. found that higher chronic pain intensity predicted more severe anxiety symptomatology. Ferguson and Ahles reported that anxiety increased the likelihood of reported pain, and Arntz et al. found that more anxious psychiatric patients had greater psychological responsiveness to pain. Patients with greater pain-related anxiety tended to overpredict new pain, anticipating motion exercise to be signifi-

### Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Participants Meeting Diagnostic Criteria (%)</th>
<th>Chronic Pain (n = 382)</th>
<th>General Population (n = 5495)</th>
<th>Inferential Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mood disorder</td>
<td></td>
<td>83 (21.7)</td>
<td>551 (10.0)</td>
<td>31.16 &lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>77 (20.2)</td>
<td>510 (9.3)</td>
<td>26.53 &lt;0.0001</td>
</tr>
<tr>
<td>Dysthymia</td>
<td></td>
<td>20 (5.2)</td>
<td>128 (2.3)</td>
<td>5.48 &lt;0.01</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td></td>
<td>134 (35.1)</td>
<td>992 (18.1)</td>
<td>21.54 &lt;0.0001</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td></td>
<td>28 (7.3)</td>
<td>144 (2.6)</td>
<td>9.1 &lt;0.0005</td>
</tr>
<tr>
<td>Panic disorder with agoraphobia</td>
<td></td>
<td>25 (6.5)</td>
<td>103 (1.9)</td>
<td>7.84 &lt;0.01</td>
</tr>
<tr>
<td>Simple phobia</td>
<td></td>
<td>60 (15.7)</td>
<td>456 (8.3)</td>
<td>8.7 &lt;0.01</td>
</tr>
<tr>
<td>Social phobia</td>
<td></td>
<td>45 (11.8)</td>
<td>428 (7.8)</td>
<td>5.91 &lt;0.05</td>
</tr>
<tr>
<td>Agoraphobia with or without panic</td>
<td></td>
<td>32 (8.4)</td>
<td>182 (3.3)</td>
<td>6.52 &lt;0.05</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td></td>
<td>41 (10.7)</td>
<td>182 (3.3)</td>
<td>16.29 &lt;0.001</td>
</tr>
</tbody>
</table>
cantly more painful than those with less pain-related anxiety. Chronic pain sufferers were also more inclined to be hyper-vigilant about pain as the object of their anxiety. Anxiety seldom occurs in isolation from other affective states. It has repeatedly been shown to coexist with depression and with chronic pain. In 1000 enrollees in a health maintenance organization, those with pain had higher levels of both anxiety and depression. Pain, anxiety, and depression all co-occurred in 80 general medical patients in a study by Levenson et al. McWilliams et al. have described a spectrum of anxiety disorders in patients with chronic pain (Table 1). The most prevalent anxiety disorders in the general population are simple phobia followed by social phobia; both are more common in patients with chronic pain than in the general population. Prevalence data for distinct anxiety types in patients with chronic pain has also been studied by Fishbain et al. where they found generalized anxiety disorder to be the most prevalent, seen in approximately 15% of subjects. Including generalized anxiety disorder, adjustment disorder with anxious mood, obsessive compulsive disorder, posttraumatic stress disorder and agoraphobia, the prevalence of clinical anxiety among the population with chronic pain may be as high as 60%. 

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### Assessment of Anxiety in Pain

Pain is often viewed as the presenting symptom of a medical ailment, and coexisting affective symptoms such as anxiety or depression may easily be overlooked. Psychological and psychiatric aspects of somatic disorders, however, are gaining wider appreciation with increasing availability of psychometric instruments that help delineate them.

It is not unusual for patients with chronic pain to complain of anxiety focused on the negative meaning or consequences of their pain. Like the patient with agoraphobia who avoids leaving the house, patients in pain often avoid activities they believe will increase their pain, creating a conditioned behavioral cycle of avoidance that can become severe. Anxious patients may describe feelings of unreality or dissociation, fear of losing control, difficulties with concentration, psychic tension, nervousness, or excessive worry, and may feel “stuck” on a particular thought or idea. Feelings of hopelessness and despair are also common. Chronic anxiety may impair function, affecting an individual’s work and social activities as well as physical health.

Anxiety may manifest through repetitive compulsions, avoidance, hyperventilation, restlessness, sleep disturbance, and irritability. Patients who experience anxiety may describe a wide range of physical symptoms including difficulty breathing, racing heartbeat, palpitations, chest pain, muscle tension or tightening, sweating, trembling, shaking, tingling, numbness, queasiness, abdominal distress, headaches, backaches, dizziness, unsteadiness, and other discomforts. Assessing anxiety may require obtaining descriptions of situations that provoke or rekindle anxiety symptoms, the frequency of symptoms, responses when anxious or fearful, and the impact of anxiety on activities. Thorough exploration of psychosocial history and culture can be pivotal in accurately assessing anxiety in a patient with chronic pain.

Tests, questionnaires, or inventories are other means by which cognitive components of anxiety may be assessed in patients with chronic pain. Several instruments specifically address anxiety in chronic pain. The Fear of Pain Inventory developed by McNeil et al. measures levels of fear related to a number of hypothetical pain-inducing events. In 1986, Reiss et al. developed the Pain Sensitivity Index to measure cognitive traits that relate to the fear of pain. McCracken et al. also in 1992, introduced the increasingly popular Pain Anxiety Symptoms Scale, which differs from other pain-anxiety assessing instruments in that it attempts to measure and examine anxiety from a behavioral perspective. Despite these specific instruments, the most popular psychometric questionnaire for assessing anxiety across large populations to date, including patients with chronic pain, remains the State-Trait Anxiety Inventory. This inventory distinguishes between dispositional or trait anxiety, and situational or state anxiety. Despite its wide use, it has been criticized for gaps that may leave important features of anxiety unassessed.

### Psychological Mechanisms

#### Psychological Mechanisms

The psychological pathways leading to anxiety disorders, as well as the exact means by which anxiety and pain impact each other, are not yet fully clarified. Explanations based upon classic learning theory, the cognitive information-processing model, and the operant conditioning model are the most common to date.

Classic learning theory suggests that anxiety develops as a response to non-threatening situations because the individual has been punished in the past during those situations. Once conditioned, the individual will seek to escape or avoid such situations. As long as the conditioned stimulus is avoided, this behavior cannot be extinguished, i.e., the learned anxiety response will be maintained. Many current exposure therapy methods are based upon this model.

Theoreticians have increasingly implicated cognitive information-processing as a basis for pathological anxiety. Although details vary between authors, the core premise is that anxiety symptoms result from a pattern of selective processing that favors threatening information. Patients with excessive anxiety may lack the ability to negate or reverse these automatic patterns.

Common components of maladaptive anxiety within patients with pain appear to be the tendency toward hypervigilance or catastrophizing. These tendencies may amplify the individual’s perception of pain through processes similar to what we know as self-fulfilling prophecies, in which individuals learn to anticipate a worst-case scenario. Evidence suggests that kinesiophobia, the tendency to worry about reinjury or fear of movement associated with pain, is also correlated with chronic pain. Picavet et al. found that both pain catastrophizing and kinesiophobia predict higher levels of back pain and disability. Fear and anxiety can also maintain pain behavior. Fordyce described a model of operant conditioning that explained the persistence of pain behaviors, even after physical healing, as a result of previously successful attempts to escape pain. This fear-avoidance model incorporates behavioral, cognitive, and physiological influences on avoidance behaviors. Asmundson et al. suggested that an individual who develops negative expectations regarding the harmfulness of his or her pain may also develop fear of pain or situations that have become associated with the pain experience. As a result, fear initiates avoidance
behaviors that eventually contribute to deconditioning and thereby perpetuate pain experiences, negative expectancies, and avoidance.38

**Biological Mechanisms**

Physiological mechanisms of anxiety have been studied intensely with a complex literature too voluminous to survey here. Much research suggests that there are biologically based, inborn temperamental predispositions to severe anxiety.39,40 The same may be true for chronic pain states. To date, exploration of the neurobiology of anxiety and associated disorders have disclosed many relevant pathways and mechanisms. These involve monoamines, gamma-amino-butyric acid (GABA), glutamate, adenosine, cannabinoids, putative endogenous benzodiazepine modulators, as well as numerous other neuropeptides, hormones, neurotrophins, cytokines, and other molecules41—a "menu" that has substantial overlap with mediators of chronic pain. Brain imaging and mapping studies of anxiety states suggest activation of the amygdala, hippocampus, orbital frontal cortex, and other regions of prefrontal cortex.42–44 Neuroimaging studies of chronic pain states and of chronic states marked by depression, anxiety, or fear reveal overlapping areas of brain activation.45–47 Taken together, these data suggest that suffering associated with anxiety, fear, and pain is related to activation of overlapping brain circuits during these three experiences.

How anxiety amplifies pain is not exactly clear. The sympathetic nervous system is a potential link between pain and anxiety: stimulation of the sympathetic nervous system lowers nociceptive thresholds and increases spontaneous activity of nociceptors and neurones.48–50 Sympathetic maintenance of pain has been recognized since the U.S. Civil War. Anxiety is associated with sympathetic nervous system arousal, including heightened activity of medullary chemoreceptors involved with respiratory drive and modulation.51 Carr and Sheehan first proposed the model of the faulty "suffocation alarm" for panic disorder based on observations of aberrant responses of patients with panic disorder to challenge with intravenous lactate or inhaled CO2.51

Stress has been demonstrated to down regulate benzodiazepine (BNZ) receptors in the frontal cortex as well as to activate the hypothalamic-pituitary-adrenal (HPA) axis, responses that may predispose to pain, anxiety or both.41 HPA overactivity has been associated with anxiety states as well as with endogenous opioid-mediated descending analgesia. Receptors for corticotrophin-releasing factor are concentrated in brain areas such as the amygdaloid nucleus and cingular cortex believed to be involved both in anxiety and pain.41

Conditioned fear responses appear to be processed by circuits related to the central nucleus of the amygdala, whereas nonconditioned anxiety appears to be processed through a nearby but distinct area within the stria terminalis.52 Common manifestations of anxiety and fear may relate to these disparate pathways converging in overlapping areas of the hypothalamus and brainstem. Ballenger has suggested that the central nucleus of the amygdala may have a role in specific conditioned stimuli such as may underlie social phobia.53 Alternatively, problems within the stria terminalis may lead to "free-floating" symptoms that are independent of specific stimuli, such as in generalized anxiety.53

**Treatments**

Anxiety can be effectively treated psychologically, pharmacologically, or with a combination of both. At present, psycholog-
studies have shown promising results with this cognitive-behavioral approach in the chronic pain population. Vlaeyen et al. found in chronic pain patients that graded exposure in vivo, but not graded activity, led to fear reduction. Investigating the short-term effects of an exposure in vivo treatment procedure, Boersma et al. found clear decreases in fear ratings and avoidance beliefs among a pain population.

Attention-Diversion. Since attention is believed to have limited capacity, its focusing upon some stimuli is thought to divert from all others. In patients with chronic pain, attention-diversion involves the application of competing external stimuli. These applications can range from utilizing passive external stimuli to having the patient perform active physical tasks. Pickett and Clum found attention-redirection to be more effective than relaxation training, relaxation instruction, and no treatment for postsurgical anxiety.

Cognitive Reappraisal. Cognitive reappraisal involves altering negative thoughts or replacing them with positive alternatives. During such therapy, an individual is trained to recognize and identify catastrophizing statements, dispute them, find evidence against them, and replace these statements with more adaptive alternatives. Following hysterectomy, patients taught cognitive control over anxiety demonstrated decreased levels of distress and pain compared to control groups.

Hypnosis. In children, both direct and indirect suggestions of pain relief significantly reduce pain and anxiety during lumbar puncture. Hypnosis produced pain relief in 68% of 37 adult patients hospitalized for various medical diseases. Adults with chronic pain referred for pain management demonstrated improvement within two to three sessions of training in self-hypnotherapy. In general, hypnosis appears helpful for pain, although this technique is most likely moderated by client variables such as age and suggestibility.

Systematic Desensitization. This approach works by “reciprocal inhibition,” where the replacement of tension with relaxation takes place through gradual steps. It is unproven in its efficacy or superiority to any other methods. Kondas and Scetnicka, however, found that systematic desensitization reduced anxiety and pain in pregnant women with heightened anxiety about childbirth.

The overlap of analgesic and anxiolytic pharmacotherapies is striking.

Pharmacotherapy

Among the many pharmacological strategies for anxiety include agents such as benzodiazepines, traditional and atypical antidepressants, or other medications that fall into the realm of membrane-stabilizing or mood-stabilizing agents such as anticonvulsants. The scope of this article precludes covering the full spectrum of anxiolytic psychopharmacology. However, the overlap of analgesic and anxiolytic pharmacotherapies is striking. Figure 1 presents two overlapping circles, each with the major drug groups used in psychiatry and pain management, respectively. As demonstrated by the overlap of the two circles, there are no major psychiatric drug groups that are not also used for analgesia, particularly for neuropathic pain. These drugs include antidepressants, benzodiazepines, and mood/membrane stabilizers such as anticonvulsants. This overlapping of therapeutic effect is unlikely to be a coincidence: the algesic effect of anxiety and other major affective disorders, and the analgesic effects of treating anxiety and other affective states, would predict this overlap. New medications, such as pregabalin and duloxetine, hold promise as single agents that treat disorders that comprise anxiety and pain as comorbidities.
Summary

Rigorous studies on the interactions between anxiety and pain are still in their infancy. Still, much progress has been made in understanding the impact of anxiety and fear upon chronic pain. Why some patients respond favorably to pharmacological approaches while others respond better to psychological interventions or a combination of both is not clear. Nonetheless, optimal care of patients with chronic pain requires an appreciation of the interplay between anxiety and pain and the interplay between anxiety and analgesia.

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REFERENCES


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