SCIENTIFIC & MEDICAL WRITING

Antidepressants & Inflammation

TEST A | Evidence Synthesis & Newsletter Copy

ASSIGNMENT

Using the provided source material, develop concise **Issue, Actions, and Benefits** statements and write a **front-page teaser of 40 words or fewer**.

MY DELIVERABLE

ISSUE

Prolonged stress, anxiety, and depression can promote persistent inflammatory activity, increasing the risk of adverse physical health effects.

ACTIONS

Understanding the relationship between chronic stress, inflammation, and psychiatric disorders can help physicians recognize therapeutic strategies that target both psychiatric symptoms and inflammatory activity.

BENEFITS

By reducing persistent inflammatory activity, antidepressants may provide benefits beyond psychiatric symptom relief and potentially reduce the adverse physical effects associated with chronic stress.

NEWSLETTER TEASER

“We tend to think of stress, anxiety, and depression as matters of the mind. But what if their effects extend far beyond the brain? And could the same be true of antidepressants?”

Provided source material: *Worried Sick: Antidepressants as Anti-Inflammatory Agents*
The complete source material provided for this writing task appears on the following two pages.

Worried Sick: Antidepressants as Anti-Inflammatory Agents

Anxiety and depression: It's not just in your head

R. Bruce Lydiard, MD, PhD
Director of Southeast Health Consultants, Inc.

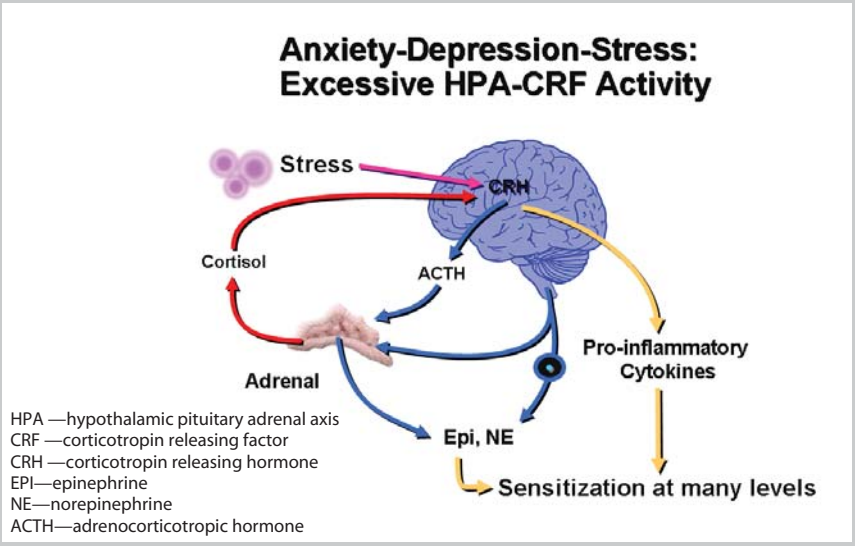
Issue
Actions
Benefits

Persistent, uncontrolled stress is associated with the development of cardiovascular, immune, and metabolic disorders, including hypertension, atherosclerosis, type II diabetes, abdominal obesity, and other medical problems.[2,3] Stress is operationally defined as perceived threat in combination with a perceived lack of control over the stressor.[2] From a clinical perspective, both anxiety disorders and depression also fulfill this operational definition of stress. Thus, in addition to being worsened by and even caused by stress, anxiety and depression are themselves stressors. Accruing evidence indicates that medical disorders known to be related to persistent stress are also associated with these psychiatric disorders.

Anxiety, depression, and stress: more alike than different?

Clinicians are keenly aware of the enhanced stress reactivity of patients with anxiety and mood disorders. The acute stress response is mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic neurons release corticotrophin-releasing factor (CRF), leading to increases in plasma cortisol and catecholamine levels. At the same time, peripherally released CRF activates the immune system, causing the release of pro-inflammatory cytokines (interleukin 1, interleukin 6, tumor necrosis factor-alpha).[3,4] When the acute stress resolves, the stress response is shut off by cortisol acting at the glucocorticoid (GC) receptors in the hypothalamus and pituitary. This feedback inhibition loop plays a critical anti-inflammatory role by turning off the stress response and stopping release of stress mediators (Figure 1).[3]

Figure 1



Activation of the HPA axis results in increased cortisol production, catecholamine release, and an acute increase in pro-inflammatory cytokine release. This process is terminated by cortisol at the glucocorticoid receptor in the brain; when stress is severe or persistent, the stress system is not completely shut down, allowing for continued release of stress mediators.

Paradoxically, pro-inflammatory cytokines and other humoral mediators of inflammation potently stimulate HPA axis and extra-hypothalamic CRF release. The resulting neural sensitization at multiple levels leads to amplification of the inflammatory response to each subsequent stressor.[4] To make matters worse, pro-inflammatory cytokines antagonize GC receptor function, thereby interfering with the GC-mediated feedback inhibition necessary to shut off CRF release.[5] With repeated or chronic stress, this self-promoting cycle makes it increasingly difficult to return to normal HPA axis functioning.

Persistent anxiety and depression are health risks

Inability to shut off the stress response disrupts the finely-tuned hypothalamic modulation of neuronal, neuroendocrine, and immune systems which function to protect our health in the short term.[2,3] Prolonged or repeated activation of the stress axis ultimately results in a self-perpetuating cycle of enhanced stress reactivity and persistently increased inflammatory activity in chronically stressed, anxious, and/or depressed individuals. Beyond the contribution to neurodegenerative effects on key stress-mediating areas of the brain such as the hippocampus,[6] loss of effective control of the stress enhances the development of a variety of medical disorders, including cardiovascular disease (atherosclerosis and coronary artery disease), metabolic disorders (insulin resistance, abdominal obesity, bone demineralization), immunologic dysfunction (susceptibility to infection, autoimmune disease), and neuroendocrine disorders.[7-9]

Worried sick

Is worrying itself actually harmful to your health? There is abundant clinical evidence that humans experiencing negative emotions or stress exhibit increased synthesis and release of proinflammatory cytokines.[1] This represents one possible mechanism by which depression may contribute to the acceleration of atherosclerosis and subsequent cardiovascular morbidity and post-myocardial mortality.[7] Less widely known is that anxiety disorders confer the same risk as depression for cardiovascular morbidity and mortality.[1] Anxiety disorders also confer increased risk for other medical disorders. Harter and colleagues conducted

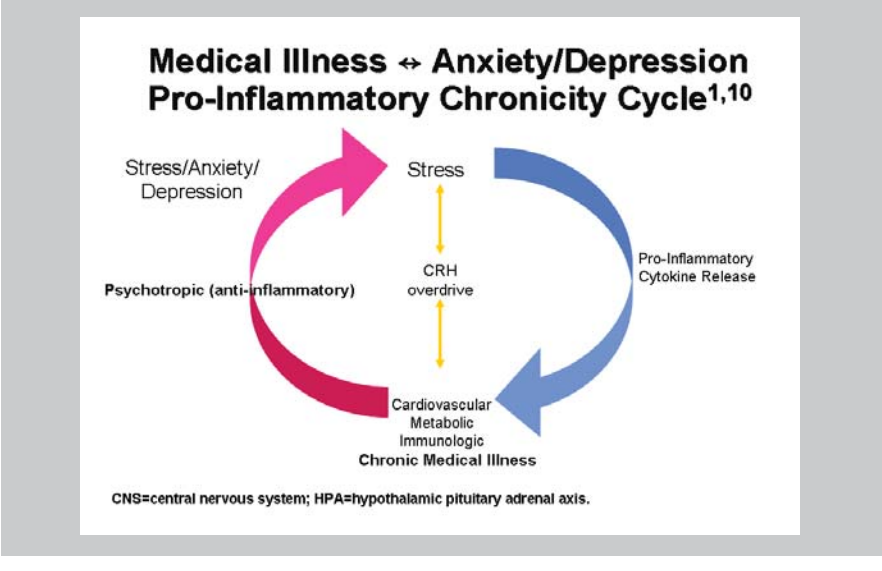
a survey of comorbidity of anxiety disorders and medical illness that controlled for gender, depression, and substance abuse. Individuals with panic disorder or generalized anxiety disorder reported two to six times higher rates of cardiac disorders, hypertension, respiratory and genitourinary problems, and migraine than those without anxiety. The findings were not likely to represent over-reporting, since only 4 of 14 conditions surveyed were significantly higher than those with anxiety disorders.[7] These findings have public health implications: could early detection and treatment of anxiety disorders and depression improve long-term health outcome? We won't know until long-term research sheds some light on this important question.

Cytokines and the sick syndrome

A dramatic demonstration of the potent brain effects of pro-inflammatory cytokines are the effects of therapeutic pro-inflammatory cytokine immune therapy in humans. Patients receiving interferon-alpha frequently experience anhedonia, anorexia, social withdrawal, fatigue, anxiety, and depressed mood. This cytokine-induced "sick syndrome" closely resembles major depression.[4,8-12]

Pre-treatment with antidepressants can attenuate or prevent the appearance of these symptoms. Based on these findings, some investigators postulate that these inflammatory mediators play a role in the etiology of major depression.[9] One proposed mechanism by which cytokines may influence affective states is by modifying HPA axis reactivity and neurotransmitter release in a fashion that resembles the stress response.[4] Furthermore, synergy of released pro-inflammatory cytokines with psychogenic and neurogenic stressors has been demonstrated. Synergy has also been demonstrated with combined "subthreshold" doses of cytokines that alone have no effects but in combination can activate the HPA axis.[3] Analogous to repeated stress, repeated release of pro-inflammatory cytokines elicits increasingly greater neural sensitization not only in the HPA axis but also in critical neuronal circuits in the brain that modulate the stress response (Figure 2).[11]

Figure 2



Antidepressants can attenuate the effects of pro-inflammatory cytokines via reduction in synthesis, altered ratios of pro- and anti-inflammatory cytokine production, by corrective effects on the stress axi, or possibly all of the above.

Anti-inflammatory Effects of Anti-depressants

Antidepressants of several classes reduce cytokine production by immune cells in vitro,[9,10] in animal models of stress-induced depression,[11] and in depressed patients.[12] In depressed humans, several antidepressants have also been shown to reduce levels of proinflammatory cytokines and also to increase the production of anti-inflammatory cytokines, thus tilting the ratio of anti-inflammatory to pro-inflammatory activity in a favorable direction.[10,12]

Consistent with the stress-diathesis model of depression, cytokine synthesis and release provokes neuroendocrine and brain neurotransmitter changes that are interpreted by the brain as being stressors and contribute to the development of depression.[4] Agents currently in the development pipeline such as CRF antagonists may be especially helpful for individuals with excessive cortisol secretion (e.g., melancholic depression, chronic anxiety, or stress).[3]

New research is now beginning to shed light on how we can literally worry ourselves sick.

While it is unlikely that pro-inflammatory and anti-inflammatory cytokines will tell the whole story, emerging evidence increasingly suggests that anxiety and depression, like stress, may promote pro-inflammatory states with health effects occurring well beyond the brain. The medical literature has described patients with syndromes that include complaints of emotional distress, muscle pain, fatigue, and gastrointestinal discomfort for centuries. These patients have received often derogatory labels including hysteria, neurasthenia, and hypochondriasis. New research is now beginning to shed light on how we can literally worry ourselves sick.

The bottom line—The concept of mind-body separation is no longer a tenable model. Anxiety and depression, like stress, can have wide-ranging physiological effects that are potentially harmful to your health. Antidepressants can therefore benefit the whole body as well as the brain.[6] By normalizing GC receptor-HPA axis function, antidepressants exert "anti-inflammatory" effects by reducing the persistent release of humoral mediators of inflammatory activity which can contribute to long-term adverse health outcomes. Understanding the physiology of neuro-endocrine-immune function can help guide the developments of better treatments in the future.

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SCIENTIFIC & MEDICAL WRITING

Fibromyalgia

TEST B | Evidence Synthesis & Newsletter Copy

ASSIGNMENT

Using the provided source material, develop concise **Issue, Actions, and Benefits** statements and write a **front-page teaser of 40 words or fewer**.

MY DELIVERABLE

ISSUE

Fibromyalgia causes widespread pain, yet its biological basis has been poorly understood and its symptoms often dismissed as psychosomatic.

ACTIONS

Reviewing psychophysical and imaging evidence of altered pain processing in patients with fibromyalgia can clarify its biological basis and the role of neural pathways that regulate pain transmission.

BENEFITS

Understanding fibromyalgia as a real, centrally mediated pain disorder can help clinical practitioners validate patients' experiences and better understand associated problems with sleep, mood, and anxiety.

NEWSLETTER TEASER

"Fibromyalgia pain is real, yet its biological culprit has long played a Where's Waldo?-like game with clinicians. With growing evidence pointing to altered pain processing, could we finally be looking in the right place?"

Provided source material: *The Mystery of Fibromyalgia, Part 1 - Is fibromyalgia real pain, and what causes it?*
The complete source material provided for this writing task appears on the following two pages.

- Second Messenger -

The Mystery of Fibromyalgia

Part 1—Is fibromyalgia real pain, and what causes it?

Katherine J. Carpenter
NEI Staff Writer

Issue

Actions

Benefits

Attitudes among clinical practitioners about fibromyalgia range from "it's all in the mind" to "it's all in the joints." That is, that fibromyalgia is a psychosomatic condition that reflects life crises and that it is an autoimmune rheumatoid condition that affects the joints and muscles. The discovery that antidepressants can reduce pain in fibromyalgia seems to suggest that the "all in the mind" theory is correct; that fibromyalgia is caused by depressed mood. In fact, fibromyalgia is not in the mind, but in the brain, caused by aberrant processing in the pain transmission pathway. The antidepressants that are effective treatments target these pain pathways and have effects independent of their antidepressant properties.

This is the first part of a two-part article that addresses some common questions about fibromyalgia. This first installment reviews experts' current understanding of this painful and destructive condition and its possible biological basis.

Is fibromyalgia real pain?
The short answer is "yes." The longer answer includes evidence from pathological, psychophysical, and imaging studies.

Fibromyalgia has an estimated prevalence of 2% and is more common in women than men.[1] It is diagnosed by a history of widespread pain in all four body segments, and pain in 11 of 18 tender point sites on digital palpation. Although pain is felt in these tender muscle and joint sites, no identifiable pathology has been found here. About one-third of patients with fibromyalgia also meet criteria for major depressive disorder. Anxiety disorders, low self-esteem, difficult family circumstances, and poverty are not uncommon, and patients have often seen many practitioners over many years before arriving at a diagnosis of fibromyalgia. These factors, along with the absence of any identifiable pathology, led many experts to see fibromyalgia's physical symptoms as psychosomatic manifestations of unconscious conflicts, and sufferers as difficult, malingerers, and catastrophizers.

Reduced activity in descending 5-HT and NE pathways would reduce the inhibitory controls, allowing non useful and uninformative pain signals to get through the "gate."

However, there is now much evidence that pain in fibromyalgia is very real and associated with measurable changes in pain processing systems: (1) Patients with fibromyalgia perceive a painful stimulus as more painful than healthy controls do, a phenomenon known as "hyperalgesia;"[2,3] (2) In healthy, pain-free controls, repeated application of a painful stimulus causes a progressive increase in the perceived pain intensity (wind-up pain or central sensitization); this increase is greater in fibromyalgia patients;[2-4] (3) Imaging studies have shown that when the same painful stimulus is applied, there is increased activity in pain processing brain centers in patients with fibromyalgia compared with normal controls.[5]

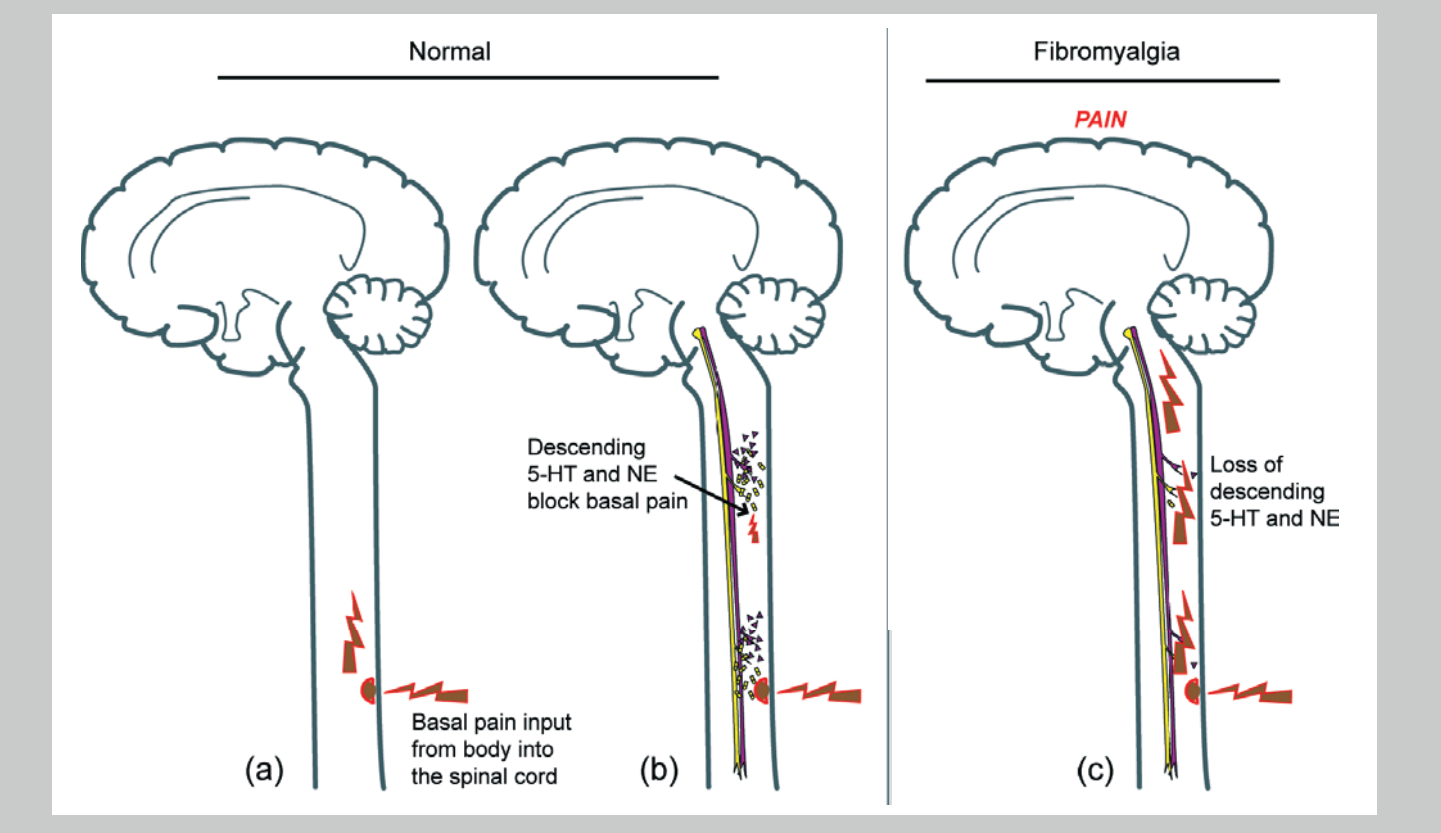
These measurable alterations in pain processing support the concept that the pain of fibromyalgia is real, slowly replacing the concept that the pain is psychosomatic.

What causes it?
If fibromyalgia is not a psychosomatic illness, and is not caused by damage to muscles or joints, what does cause it? The best explanation we have currently is aberrant processing in the pain pathway. A state of "central sensitization," seems to exist in patients with fibromyalgia, where pain signals coming in from the periphery to the spinal cord are inappropriately augmented, probably as a result of deficient descending inhibitory controls.

Neurons in the pain pathway run from the periphery (skin, joints, viscera), into the spinal cord, where they synapse with projection neurons that ascend to relay centers like the thalamus, hypothalamus and brainstem nuclei, and from there to higher centers where the location and intensity of pain is deciphered (the somatosensory cortex) and emotional and motivational aspects generated (amygdala, cingulate, and prefrontal cortex). At many points in this pathway, but particularly in the spinal cord, the basic pain signal is open to modulation, both augmentation and inhibition. One important inhibitory pathway is the opioid pathway, which descends from the brainstem to the spinal cord. It is recruited in times of severe physical and physiological stress, acting as an endogenous pain killer when the body needs to function through severe pain. The other major descending inhibitory pathways are the serotonin (5-HT) and norepinephrine (NE) pathways. These seem to be active mostly in basal conditions, damping down transmission of small, everyday noxious events that arise just from normal functioning of the human body.

This "brake" is hypothesized to be lacking in patients with fibromyalgia: reduced activity in descending 5-HT and NE pathways would reduce the inhibitory controls,

Figure 1



(a) Normally, basal pain signals arrive in the spinal cord from the body. (b) Descending serotonin (5-HT) and norepinephrine (NE) pathways inhibit the pain signal, preventing these every day inputs from being detected. (c) In fibromyalgia, the descending 5-HT and NE inhibitions may be lost, allowing every day pain impulses to ascend the spinal cord and be perceived as widespread pain.

allowing nonuseful and uninformative pain signals to get through the "gate" (Figure 1). The increased incoming barrage inappropriately activates processes that are designed to augment pain signals in times of need. A state of "central sensitization" results, giving greater output (from the spinal cord to higher centers) for a given level of input. This explains the observations of hyperalgesia and greater magnitude of wind-up in fibromyalgia patients. Accordingly, levels of 5-HT and NE metabolites in cerebrospinal fluid and serum have been shown to be reduced in fibromyalgia patients,[6] lending more evidence to the theory of insufficient 5-HT and NE.

The emotional anguish of pain (as well as the long journey to an accurate diagnosis) is likely to have psychological ramifications.

Psychological aspects are still important in fibromyalgia, and depression and anxiety occur in many patients. These may arise as direct consequences of the ongoing pain, or may even result from the same 5-HT and NE deficiency that could underlie the pain. Physical consequences of unrelenting pain can include muscle wasting and deconditioning; physiological consequences include changes in the hypothalamic–pituitary–adrenal (HPA) axis and reduced immune function; vegetative consequences include poor, unrestorative sleep and insomnia; and the emotional anguish of pain (as well as the long journey to an accurate diagnosis) is likely to have psychological ramifications, leading to depression and anxiety.

Reciprocal interactions likely occur between these circuits, which all use 5-HT and NE as important transmitters. It must not be forgotten that 95% of fibromyalgia sufferers are women, suggesting the existence of a sex difference that predisposes to fibromyalgia.

The bottom line—Fibromyalgia is a real and painful condition that is probably caused by inappropriate augmentation of pain transmission at a central site, likely the spinal cord. This may be due to reduced activity of descending serotonin and norepinephrine pathways. Complicated overlap exists between these pain pathways and other important monoaminergic pathways, possibly underlying problems fibromyalgia patients have with sleep, mood, and anxiety.

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