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Review Article

CNS Depressants and Anti-Inflammatory Medications Used in Fibromyalgia Disease

Usha Verma*, Sanjita Das and Saumya Das

Department of Pharmacology, NIET, Greater Noida, India.

ABSTRACT

Fibromyalgia is an idiopathic, chronic pain syndrome defined by widespread nonarticular musculoskeletal pain and generalized tender points. Mood disturbance is common among patients with fibromyalgia (FM), but the influence of psychological symptoms on pain processing in this disorder is unknown. In this approach, some kind of manipulations are conducted to induce clinically relevant pain states such as hyperalgesia and allodynia in the experimental animal, and then, pain-associated behaviors are measured as indicators of pain. Recent findings regarding sleep architecture, immunology, and endocrinology have provided clues that may help in the understanding and resultant treatment of this entity. Women with fibromyalgia tend to present with an alpha-delta sleep anomaly, which when treated with a growth hormone secretagogue (GHS), reduces the rheumatological pain and restores slow-wave sleep architecture. Efficacy of test drugs on the said pain is finally evaluated. Diazepam and ibuprofen relieves anxiety and inflammation respectively in fibromyalgia. The selected NSAIDS and CNS depressants as a combination therapy are frequently used prescription agents for fibromyalgia. Though the above mentioned treatment profile is for fibromyalgia, antidepressants and NSAIDS are the more frequently used combination therapy for this disease.

Keywords: Fibromyalgia, CNS Depressants, Anti-Inflammatory, NSAIDS, Anti-Oxidants.

INTRODUCTION

Fibromyalgia is a chronic condition characterized by pain in the muscles, ligaments, and tendons; fatigue, and multiple tender points on the body (Abeles et al., 2008). There is evidence that people with the condition may be more sensitive to pain because something is wrong with the body's usual pain perception processes (Bennetet al., 2009). It also tends to coexist with sleep disorders, anxiety, depression and irritable bowel syndrome historically, fibromyalgia has been considered either a musculoskeletal disease or neuropsychiatric condition (Bernardy et al., 2011). Though the above mentioned treatment profile is for fibromyalgia, antidepressants and NSAIDS are the more frequently used combination therapy for this disease. The disease onset appears to follow physiological and/or psychological stressors and involves a subset of symptoms that are consistent with varied disorders found in multiple medical specialties to include rheumatology, immunology, endocrinology, neurology, and psychiatry. Pain in FM is consistently felt in the musculature and is related to sensitization of central nervous system (CNS) pain pathways. Although not specific for FM, abnormal concentration of CNS neuropeptides, biogenic amines, and alterations of the hypothalamic-pituitary-adrenal axis have been described. There is a large body of evidence for a generalized lowering of pressure pain thresholds in FM patients, but the mechanical pain hypersensitivity (allodynia) of FM patients is not limited to tender points and appears to be widespread.

CLASSIFICATION

Fibromyalgia is classed as a disorder of pain processing due to abnormalities in how pain signals are processed in the central nervous system. The

International Classification of Diseases (ICD-10) lists fibromyalgia as a diagnosable disease under "Diseases of the musculoskeletal system and connective tissue" and states that fibromyalgia syndrome should be classified as a functional somatic syndrome rather than a mental disorder. Although mental disorders and some physical disorders commonly are co-morbid with fibromyalgia especially anxiety, depression and irritable bowel syndrome and chronic fatigue syndrome the ICD states that these should be diagnosed separately (Hauser et al., 2009).

1. "extreme sensitivity to pain but no associated psychiatric conditions" (may respond to medications that block the 5-HT3 receptor)
2. "fibromyalgia and comorbid, pain-related depression" (may respond to antidepressants)
3. "depression with concomitant fibromyalgia syndrome" (may respond to antidepressants)
4. "fibromyalgia due to somatization" (may respond to psychotherapy)

SIGNS AND SYMPTOMS

The defining symptoms of fibromyalgia are chronic widespread pain, fatigue, and heightened pain in response to tactile pressure (allodynia) (Table 1). Other symptoms may include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations, functional bowel disturbances, and chronic sleep disturbances, (Moldofsky et al., 1975).

Table 1: Associated Signs and Symptoms of FMS

Sign or Symptom	% of Patients
Widespread pain	97.6
Tenderness at >11 of 18 specific tender points	90.1
Fatigue	81.4
Morning stiffness	77.0
Sleep disturbance	74.6
Headache	52.8
Anxiety	47.8
Dysmenorrhea history	40.6
Sicca symptoms	35.8
Previous depression	31.5
Irritable bowel syndrome	29.6
Urinary urgency	26.3
Raynaud's phenomenon	16.7

PATHOPHYSIOLOGY

Fibromyalgia is currently understood to be a disorder of central pain processing or a syndrome of central sensitivity. Clauw also suggests that patients may have hypersensitivity because of neurobiologic changes that affect the perception of pain or because of expectancy or hypervigilance, which may be related to psychological factors (Clauw et al., 1995).

Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey et al., 1986). Although normally adaptive, the stress response may become maladaptive in patients with chronic pain and fatigue syndromes such as fibromyalgia (Pilleme, Crofford, Martinez and Tanriverdi, 2007). The important biologic elements here include proinflammatory cytokines, the HPA axis, other neuroendocrine axes, and the autonomic nervous system (figure1). Growth hormone abnormalities are also thought to contribute to symptoms in fibromyalgia (Jones et al., 2007).

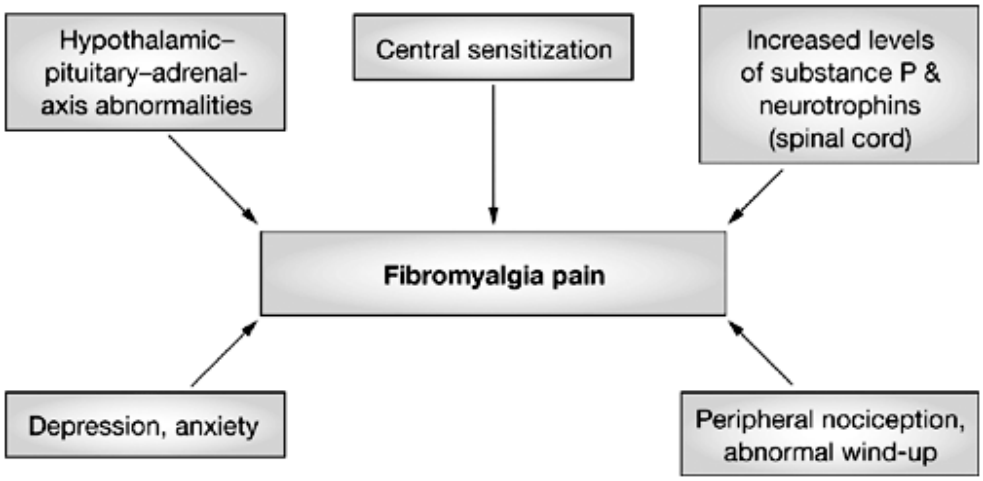

Fig. 1: Pathogenesis of pain in fibromyalgia syndrome

A number of abnormalities in pain processing have been demonstrated in fibromyalgia. Among them are the following (Clauw, Staud, Wood and Nardi, 2007):

- Excess excitatory (pronociceptive) neurotransmitters (e.g. substance P, glutamate levels in the insula)
- Low levels of inhibitory neurotransmitters (e.g. serotonin and norepinephrine) in descending antinociceptive pathways in the spinal cord
- Maintained enhancement of temporal summation of second pain
- Altered endogenous opioid analgesic activity in several brain regions known to play a role in pain modulation
- Dopamine dysregulation

Central processes

Plasticity in the function of *N* -methyl-*D* -aspartate (NMDA) subtype glutamate receptors is necessary for central sensitization to occur. Increased sensitivity of central NMDA receptors were implicated in earlier studies as playing a primary role in fibromyalgia. However, subsequent evidence has suggested that suppression of the normal activity of dopamine-releasing neurons in the limbic system is the primary pathology in fibromyalgia. Increasing evidence indicates that fibromyalgia may represent a dysregulation of dopaminergic neurotransmission.

Serotonin

The most widely acknowledged biochemical abnormality associated with fibromyalgia is abnormally low serotonin levels. A low platelet serotonin value is believed to be the cause of the low serum levels, which have been correlated with painful symptoms. Low serotonin levels in the CNS are thought to result from low levels of tryptophan (the amino acid precursor to serotonin) and 5-hydroxyindole acetic acid (a metabolic by-product) in the cerebrospinal fluid (CSF).

Substance P

Substance P is a neurotransmitter that is released when axons are stimulated. Elevated levels of substance P increase the sensitivity of nerves to pain or heighten awareness of pain. Four independent studies have found that levels of substance P are 2 to 3 times higher than normal in the CSF of patients with fibromyalgia (Russell et al., 1994).

PHARMACOLOGICAL MEDICATIONS

In 2007 the Food and Drug Administration approved Pregabalin (Lyrica) as the first drug specifically for the treatment of fibromyalgia. Other drugs used to treat fibromyalgia are antidepressants or muscle relaxants. The use of NSAIDs are not recommended as first line therapy (Heymann et al.,). The goal has been to improve sleep and pain tolerance.

Antidepressants

Antidepressants are "associated with improvements in pain, depression, fatigue, sleep disturbances and health-related quality of life in patients with FMS" (Hauser et al., 2009). The main classes of antidepressants used for treating fibromyalgia are tricyclics, selective serotonin-reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). **Tricyclics-** Tricyclic antidepressants were the first drugs to be well-studied for fibromyalgia. They cause drowsiness and can be helpful for improving sleep. The tricyclic drug most commonly used for fibromyalgia is amitriptyline (Elavil, Endep), which produces modest benefits with pain, but can lose effectiveness over time.

Selective Serotonin-Reuptake Inhibitors- Selective serotonin-reuptake inhibitors (SSRIs) increase serotonin levels in the brain, which may have specific benefits for fibromyalgia patients. Commonly prescribed SSRIs include fluoxetine (Prozac), and fluvoxamine (Luvox) in reducing pain.

Serotonin-Norepinephrine Reuptake Inhibitors- Serotonin-norepinephrine reuptake inhibitors (SNRIs) are also known as dual inhibitors because they act directly on two chemical messengers in the brain -- norepinephrine and serotonin. These drugs appear to have more consistent benefits for fibromyalgia pain than SSRIs includes duloxetine (cymbalta), venlafaxine (Effexor).

Muscle Relaxants Cyclobenzaprine (Flexeril) relaxes muscle spasms in specific locations without affecting overall muscle function. It helps relieve fibromyalgia symptoms.

Pain Relievers

Pain relief is of major concern for patients with fibromyalgia. Pain relievers for fibromyalgia include:

- Tramadol (Ultram), used alone or in combination with acetaminophen (Tylenol), is commonly prescribed for relief of fibromyalgia pain. Its most common side effects are drowsiness, dizziness, constipation, and nausea. Tramadol should not be used in combination with tricyclic antidepressants.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are of limited efficacy in reducing pain due to fibromyalgia but are important adjuncts for nociceptive pain generators, such as osteoarthritis and degenerative spondylosis (Winfield et al., 2007).
- Capsaicin (Zostrix) is an ointment prepared from the active ingredient in hot chili peppers. Capsaicin is helpful for relieving painful areas in other disorders. It may also have some value for fibromyalgia patients.
- Opioids, or narcotics, may be used occasionally by certain patients with moderate-to-severe pain, or those with significant problems performing everyday tasks.

FIBROMYALGIA, CNS DEPRESSANTS AND NSAIDS AS A ROLE OF ANTIOXIDANT

One theory of fibromyalgia (FMS) and chronic fatigue syndrome (ME/CFS) is that oxidative stress plays a key role and possibly a causative one as well. A diet rich in antioxidants may help to relieve fibromyalgia symptoms, according to the National Institutes of Health (Adrienne et al., 2012).

Experimental data show that acute administration of diazepam results in a cascade of oxidative changes and significantly diminishes cell antioxidant defense, especially the intracellular levels of reduced glutathione. In these conditions the role of antioxidants seems predictable (Musavi et al., 2003). NSAIDs can enhance levels of antioxidant vitamins and minerals. Researchers at the Royal Infirmary in Glasgow have found that the common NSAID, ibuprofen, can help normalize antioxidant levels in people with cancer (McMillan et al., 2000).

CONCLUSION

FM is a chronic pain syndrome that is characterized by widespread pain in peripheral tissues, psychological distress, and central sensitization. Three important strategies for FM therapy appear useful at this time: reduction of peripheral nociceptive input, particularly from muscles; improvement or prevention of central sensitization; and treatment of negative affect, particularly depression. The first strategy is most likely relevant for acute FM pain exacerbations and includes physical therapy, muscle relaxants, muscle injections, and anti-inflammatory analgesics. Central sensitization can be successfully ameliorated by cognitive behavioral therapy, sleep improvement, NMDA receptor antagonists, and antiseizure medications. The pharmacological and behavioral treatment of secondary pain affect (anxiety, anger, depression) is equally important and may currently be one of the most powerful interventions for FM pain. Whether narcotics are useful for the treatment of FM pain is currently unknown because of insufficient trial experience. It concluded that factors that contribute to the pathophysiology of fibromyalgia include biologic and genetic influences, environmental triggers, and abnormal function of the neuroendocrine and autonomic nervous systems. These factors are frequently shared by persons with disorders that co-occur with fibromyalgia, such as chronic fatigue syndrome, irritable bowel syndrome, and MDD. There is no cure for fibromyalgia, but treatment aims to reduce symptoms and improve the quality of life. In future to extend this study, elaborated pharmacological studies will be done as the used synthetic drugs in fibromyalgia.

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