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IMPACT OF CNS DEPRESSANTS & NSAIDS MEDICATIONS IN FIBROMYALGIA DISEASE

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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, Diazepam, Ibuprofen, NSAIDS, Hyperalgesia, Cold stress.

INTRODUCTION

The term fibromyalgia derives from new Latin, fibro- meaning fibrous tissues, Greek myo- muscle and Greek algos- pain, thus the term literally means muscle and connective tissue

pain.[1,2] Fibromyalgia is a syndrome of persistent widespread pain, stiffness, fatigue, disrupted and unrefreshing sleep and cognitive difficulties, often accompanied by multiple other unexplained symptoms, anxiety and/or depression and functional impairment of activities of daily livings. It typically presents in young or middle-aged women. Fibromyalgia was once often dismissed by physicians and the public as a psychological disorder or "wastebasket" diagnosis because of an absence of objective findings on physical examination and usual laboratory and imaging evaluations. Many physicians still do not accept fibromyalgia as a discrete illness. However, basic and clinical investigations have clarified the neurophysiologic bases for fibromyalgia and led to its current classification as a central sensitivity syndrome.[3] Indeed, fibromyalgia can now be considered a neurosensory disorder characterized in part by abnormalities in pain processing by the central nervous system.[4]At a clinical level, fibromyalgia is much more than widespread pain. It overlaps substantially with other central sensitivity syndromes, such as the following:

- Chronic pelvic pain syndromeprimary dysmenorrheal Temporomandibular joint pain
- Tension-type headaches/migraine
- Posttraumatic stress disorder
- Multiple chemical sensitivity
- Periodic limb movement disorder/restless legs syndrome
- Interstitial cystitis

Classification

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

Differences in psychological and autonomic nervous system profiles among affected individuals may indicate the existence of fibromyalgia subtypes. A 2007 review divides individuals with fibromyalgia into four groups as well as "mixed types".[5,6]

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).[7] Other symptoms may include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations, functional bowel disturbance and chronic sleep disturbances.[8,9] such as the following:

- Widespread pain and stiffness Fatigue or trouble sleeping
- Paresthesia (tingling)
- Irritable bowel syndrome
- Skin sensitivity
- Heightened sensitivity to noises, bright lights, smells
- Depression
- Headaches
- Pain after exertion
- Memory lapses or difficulty in concentrating

Causes[10,11]

- Changes in brain chemicals
- Disregulation of the autonomic nervous system
- Sleep problems
- Psychological factors
- Physical trauma
- Small bowel bacterial overgrowth syndrome
- Candida overgrowth
- Vitamin deficiencies
- Adrenal fatigue
- Glutathione deficiency

Pathophysiology

The pathophysiology of fibromyalgia involves a number of factors, including abnormalities in the neuroendocrine and autonomic nervous systems, genetic factors, psychosocial variables, and environmental stressors.[12,13] Fibromyalgia is currently understood to be a disorder of central pain processing or a syndrome of central sensitivity . Clauw describes the

syndrome as a diffuse problem of sensory volume control such that patients have a lower threshold of pain and of other stimuli, such as heat, noise and strong odors. 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.[14]

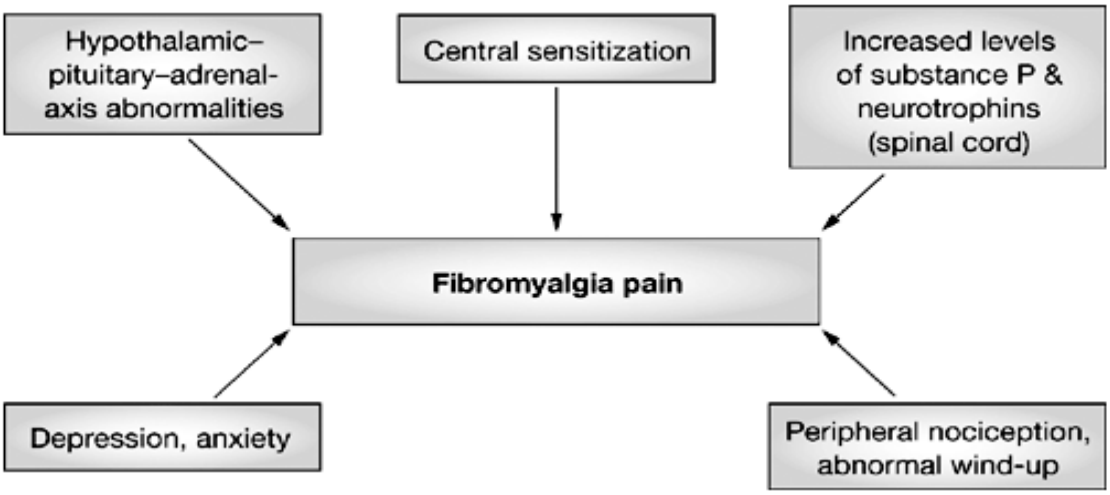

Figure no. 1: Pathogenesis of pain in fibromyalgia syndrome.

1. **Pain sensitivity in women Fibromyalgia is most common in women:** Among the mechanisms that may contribute to increased pain sensitivity in women are the following:

- Differences in primary afferent input to the central sensitization, with developmental and menstrual cycle–dependent enhancement
- Developmental and phasic gonadal-hormonal modulation of pain regulatory systems, stress-induced analgesia and opioid receptors
- Higher levels of trait and state anxiety
- Increased prevalence of depression
- Use of maladaptive coping strategies
- Increased behavioral activity in response to pain

2. **Central processes:** Plasticity in the function of N -methyl-D -aspartate subtype glutamate receptors is necessary for central sensitization to occur. Increased sensitivity of central N -methyl-D -aspartate 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.[14]The "dopamine hypothesis of

fibromyalgia" proposes that the central abnormality responsible for symptoms associated with fibromyalgia is a disruption of normal dopamine-related neurotransmission. Insufficient dopamine in a part of the body is termed hypodopaminergia. Dopamine is a catecholamine neurotransmitter with roles in pain perception and natural analgesia. There is also strong evidence for a role of dopamine in restless leg syndrome, which is a condition found frequently in patients with fibromyalgia.

3. **Autonomic nervous system:** Aberrations in autonomic nervous system functioning are often observed among patients with fibromyalgia. Abnormalities may contribute to enhanced pain and other clinical problems associated with fibromyalgia via the alteration of physiologic responses required for effective stress management (e.g., increases in blood pressure) and pain inhibition via diminished production of growth hormone and insulin-like growth factor.[15,16,17]
4. **Serotonin:** The most widely acknowledged biochemical abnormality associated with fibromyalgia is abnormally low serotonin levels. In 1992, decreased serotonin metabolites in patient blood samples and cerebrospinal fluid were reported. CHAPTER 1 INTRODUCTION Department of Pharmaceutical Technology, NIET 18 Regulation of serotonin metabolism takes place during the deep or therapeutic sleep patterns. ßWith the sleep disturbances of Fibromyalgia, the metabolic regulation is disrupted. This cause's further immune system dysfunction due to the role serotonin plays in the activation of natural killer cells. However, selective serotonin reuptake inhibitors (SSRIs) have met with limited success in alleviating the symptoms of the disorder, while drugs with activity as mixed serotonin-norepinephrine reuptake inhibitors (SNRIs) have been more successful. Many studies have linked serotonin, a neurotransmitter, to sleep, pain perception, headaches and mood disorders. Lowerthan-normal levels of serotonin have been observed in patients with fibromyalgia.[18,19] 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 central nervous system 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. Investigators have proposed a link between low serotonin levels and symptoms of fibromyalgia.[20] Indeed many propose that low serotonin levels may cause fibromyalgia in whole or in part. Serotonin is involved in multiple functions that regulate and influence:

- Sleep cycles

- Mood
- Learning
- Pain perception
- Immune system

5. **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 cerebrospinal fluid of patients with fibromyalgia. A neurotransmitter is a substance that passes signals or information across the synapse (junction) that separates one nerve cell from another. Neurotransmitters are stored in the nerve cell's end. When an electrical impulse travels down the nerve cell, it causes the release of the neurotransmitter, which then travels across the synapse and either promotes or inhibits continued electrical impulses along the nerve.[21]These elevated levels cause fairly normal stimuli to result in exaggerated nociception. Substance P is responsible for:

- Transmitting pain impulses to the brain and spinal cord.
- Producing a nerve generated impulse that dilates blood vessels.
- Causing fluid and proteins to migrate from the cells to outside the cells.

6. **Adenosine triphosphate:** Researchers have found low levels of adenosine triphosphate in red blood cells of patients with fibromyalgia. Although the significance is unknown, it has been suggested that low platelet serotonin levels can be explained if platelet adenosine triphosphate levels are also low. Adenosine triphosphate is necessary to move and then hold serotonin in platelets. More investigation into adenosine triphosphate and the link to serotonin is needed.
7. **Growth hormone:** Growth hormone, produced during delta sleep, is involved in tissue repair. Therefore, disrupted stage 4 (delta) sleep associated with fibromyalgia may account for low levels of growth hormone. Growth hormone stimulates the production of insulin like growth factor I in the liver. Some authors have found that most patients with fibromyalgia have low levels of insulin like growth factor I and that low levels are specific and sensitive for fibromyalgia.
8. **Nerve growth factor:** In some studies, nerve growth factor was found to be 4 times higher in the cerebrospinal fluid of patients with fibromyalgia than it was in the cerebrospinal fluid of individuals without the condition. Nerve growth factor enhances the

production of substance P in afferent neurons, increasing an individual's sensitivity to or awareness of pain. Nerve growth factor also may play a role in spreading or redistributing perceived pain signals.[22]

9. **Cognitive impairment:** Fibromyalgia is associated with a decline in short-term, working, episodic, semantic (predominantly verbal) and procedural (skills) memory. Imaging modalities such as single-photon emission computed tomography scanning have helped to define some of the abnormalities linked to this cognitive dysfunction. Single-photon emission computed tomography shows decreased blood flow in the right and left caudate nuclei and thalami.
10. **Sleep disruption:** Sleep dysfunction is considered an integral feature of fibromyalgia. About 70% of patients recognize a connection between poor sleep and increased pain, along with feeling unrefreshed, fatigued and emotionally distressed. Several studies have linked abnormal sleep with these symptoms. Sleep studies have shown that patients with fibromyalgia have disordered sleep physiology. Sleep dysfunction is believed to be linked to the numerous metabolic disturbances associated with fibromyalgia, including abnormal levels of neurotransmitters (serotonin, substance P) and neuroendocrine and immune substances (growth hormone, cortisol, interleukin-1) . These metabolic imbalances are thought to be responsible through impairment of tissue repair and disturbance of the immunoregulatory role of sleep for the increased symptoms associated with this sleep disorder of alpha-wave intrusion.
11. **Neuroendocrine disruption:** Patients with fibromyalgia may have alterations of normal neuroendocrine function, characterized by mild hypocortisolemia hyperreactivity of pituitary adrenocorticotropin hormone release in response to challenge and glucocorticoid feedback resistance. Low insulin-like growth factor 1 levels in some fibromyalgia patients have led to the theory that these patients may actually have a different, treatable syndrome, adult growth hormone deficienct. Other abnormalities include reduced responsivity of thyrotropin and thyroid hormones to thyroid-releasing hormone a mild elevation of prolactin levels with disinhibition of prolactin release in response to challenge and hyposecretion of adrenal androgens. These changes might result from chronic stress, which, after being perceived and processed by the central nervous system, activates hypothalamic corticotrophin-releasing hormone neurons. Chronic overactivity of these neurons could disrupt normal function of the pituitary-adrenal axis and cause an increased stimulation of hypothalamic somatostatin secretion, which, in turn, could inhibit the secretion of other hormones.

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. The goal has been to improve sleep and pain tolerance. Medications from other drug classes (such as sleeping aids and pain relievers) may also be prescribed. Patients receive drug treatments in combination with exercise, patient education and behavioral therapies. The pharmacological therapy currently recommended for fibromyalgia includes antidepressants, calcium-channel modulators, muscle relaxants and analgesics. However, many patients fail to respond satisfactorily or have side effects associated with these drugs long-term use. However, patients have difficulty in adhering to a non-pharmacological therapy based only on exercises and physical medicine. Therefore, patients are highly interested in an alternative and complementary therapy, and physicians have been routinely questioned about complementary or adjuvant forms of treatment.

Complementary and Alternative medicine

Complementary and alternative medicine is popular in patients with fibromyalgia, in part due to medical skepticism (ie, doubt in the ability of conventional medical care to appreciably alter health status). Many physicians are ignorant of, if not overtly hostile toward, complementary and alternative medicine. Patients are reluctant to inform their physician about their use of complementary and alternative medicines. This can be dangerous because of unsuspected drug-to-drug interactions. A practical approach is to inquire about complementary and alternative medicine usage, to refrain from expression of negative opinions if a particular complementary and alternative medicine treatment is relatively inexpensive and appears to be safe and to encourage whatever works in the context of the power of the placebo effect and promotion of self-efficacy for pain control.

Anti-Seizure Agents (Anti-Consultants)

The anti-convulsant drugs gabapentin (Neurontin)[23] and pregabalin (Lyrica) have been tested in fibromyalgia. Pregabalin is an anti-epileptic. Also called anti-seizure drugs and anti-convulsants, these medicines affect the chemical messenger gamma aminobutyric acid, which helps prevent nerve cells from over-firing.

Antidepressants

Antidepressants are "associated with improvements in pain, depression, fatigue, sleep disturbances and health-related quality of life in patients with fibromyalgia".[24] The goal of antidepressants in fibromyalgia should be symptom reduction and if used long term, their effects should be evaluated against side effects. The main classes of antidepressants used for treating fibromyalgia are tricyclics, selective serotonin-reuptake inhibitor and serotonin-norepinephrine reuptake inhibitors. Although these drugs are antidepressants, doctors prescribe them to improve sleep and relieve pain in non-depressed patients with fibromyalgia.

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. Other tricyclics include desipramine (Norpramin), doxepin (Sinequan), imipramine (Tofranil), amoxapine (Asendin) and nortriptyline (Pamelor, Aventyl).

Selective Serotonin-Reuptake inhibitors

Selective serotonin-reuptake inhibitors increase serotonin levels in the brain, which may have specific benefits for fibromyalgia patients. Commonly prescribed serotonin-norepinephrine reuptake inhibitors include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) and fluvoxamine (Luvox) in reducing pain.

Serotonin-Norepinephrine reuptake inhibitors serotonin

norepinephrine reuptake inhibitors 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 serotonin-norepinephrine reuptake inhibitors. Serotonin-norepinephrine reuptake inhibitors include:

- Duloxetine (Cymbalta
- Venlafaxine (Effexor)
- Milnacipran (Ixel)

Muscle relaxants

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

to the tricyclic antidepressants and has similar side effects, including drowsiness, dry mouth and dizziness.

Sleep medications

Zolpidem (Ambien) or other newer sleep medications such as zaleplon (Sonata) and eszopiclone (Lunesta) may improve sleep in patients with insomnia.

Non-pharmacological medications

The non-pharmacological treatment of fibromyalgia consists, in most cases, of patient's education, supervised aerobic physical activity and cognitive-behavioral therapy.

Physical exercises

Stimulating the practice of physical activity in patients with fibromyalgia aims to improve or maintain the patient's physical fitness; provide emotional well-being; improve the symptoms of fibromyalgia and improve health and overall well-being. Domestic chores, such as walking from home to work, cleaning the house, and removing leaves from the sidewalk among other tasks, are considered productive ways to add physical activity to patient's daily routine. Physical activity of moderate intensity, such as walking, dancing and stationary biking, is the aerobic activity that can be considered for the physical therapy of such patients. Physical exercise programs, mainly aerobic exercises with neither load nor high impact on the musculoskeletal system, such as dancing, swimming and water aerobics, greatly reduce the impact of fibromyalgia symptoms on patients' lives. Low-intensity exercises or those in which the patient can identify the limit of his/her exertion and pain seem to be the most effective. Physical activity exerts an analgesic effect by stimulating the release of endorphins, acting as an antidepressant and providing an overall well-being and self-control sensation.

Cognitive-behavioral therapy

In patients with important physical limitation due to pain or difficulty to exercise, or even with mood disorders, psychological and psychiatric intervention is required. Cognitive-behavioral therapies especially when combined with aerobic exercises, stretching and family education, have provided excellent results. A randomized and controlled study of 60 patients has assessed the efficacy of cognitive-behavioral therapy in patients with fibromyalgia. All patients received amitriptyline 25 mg/day, but only half of then underwent cognitive-behavioral therapy. The results showed that cognitive-behavioral therapy was effective when used in association with pharmacotherapy.

Advancements in the pharmacological treatment of fibromyalgia

Fibromyalgia syndrome is a chronic pain disorder of obscure etiology that afflicts an estimated four to six million adults in the United States. Although women in their third to fifth decades of life are most commonly affected, it may occur in patients of any age. Although Fibromyalgia is sometimes dismissed as a psychosomatic disorder, the adoption of diagnostic criteria by the American College of Rheumatology in 1990 has fostered patient and physician acceptance of fibromyalgia as a distinct clinical entity. This acceptance has, in turn, spurred basic research into the pathogenesis of Fibromyalgia and clinical intervention trials into symptom abatement. CHAPTER 1 INTRODUCTION Department of Pharmaceutical Technology, NIET 36 Food Drug Administration for the management of Fibromyalgia, based on their clinically meaningful and durable effect on pain in monotherapy trials. They also have been shown to beneficially effect patient global impression of change, function and variably other key symptom domains, such as fatigue, sleep disturbance and cognition.

Non-steroidal anti-inflammatory drugs (Nsaid's)

IN FIBROMYALGIA NSAID's have commonly been used to treat fibromyalgia. Fibromyalgia patients most commonly report generalized pain and stiffness. NSAID's are commonly used for their anti-inflammatory and analgesic (pain-killing) properties.[25] Unfortunately, despite their widespread use, NSAID's have not been shown to be very effective in relieving the painful symptoms of fibromyalgia. There is no documented evidence of inflammatory changes associated with this syndrome. In a study of 46 fibromyalgia patients that compared Ibuprofen to placebo, both groups reported interval improvement in fatigue, pain, tender points and subjective swelling and there was no significant difference between the two groups.[26] In another 6 week study of 62 fibromyalgia patients, groups of patients were given the tricyclic anti-depressant Amitriptyline, the NSAID Naproxen, either drugs or neither drug. Although there was initial improvement in pain at two weeks in the Naproxen group, the difference was not significant. While these studies do not demonstrate the efficacy of NSAID's for fibromyalgia patients, they may have clear benefits for fibromyalgia patients with concomitant and exacerbating conditions such as osteoarthritis, (the bones in the joint to rub against each other, creating inflammation and pain) rheumatoid arthritis (destruction of joints in the body) or other conditions.

Cns depressants in fibromyalgia

The most common type of antidepressant prescribed for fibromyalgia patients is called a tricyclic antidepressant. Antidepressants called selective serotonin reuptake inhibitors (SSRIs) are also prescribed and in some cases an SSRI and tricyclic antidepressant may both be prescribed for control of pain and fatigue in fibromyalgia. Diazepam is mainly used to treat anxiety, insomnia and symptoms of acute alcohol withdrawal. It is also used as a premedication for inducing sedation, anxiolysis or amnesia before certain medical procedures (e.g., endoscopy).

Interactions

If diazepam is to be administered concomitantly with other drugs, attention should be paid to the possible pharmacological interactions. Particular care should be taken with drugs that enhance the effects of diazepam, such as barbiturates, phenothiazines, narcotics and antidepressants. Diazepam does not increase or decrease hepatic enzyme activity and does not alter the metabolism of other compounds. No evidence would suggest diazepam alters its own metabolism with chronic administration.

Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder

The role of free radicals in fibromyalgia is controversial. In this study, 85 female patients with primary fibromyalgia and 80 age, height, and weight-matched healthy women were evaluated for oxidant/antioxidant balance. Malondialdehyde is a toxic metabolite of lipid peroxidation used as a marker of free radical damage. Superoxide dismutase is an intracellular antioxidant enzyme and shows antioxidant capacity. Pain was assessed by visual analog scale. Tender points were assessed by palpation. Age, smoking, body mass index and duration of disease were also recorded. Malondialdehyde levels were significantly higher and superoxide dismutase levels significantly lower in fibromyalgic patients than controls. Age, body mass index, smoking and duration of disease did not affect these parameters. We found no correlation between pain and number of tender points. In conclusion, oxidant/antioxidant balances were changed in fibromyalgia. Increased free radical levels may be responsible for the development of fibromyalgia. These findings may support the hypothesis of fibromyalgia as an oxidative disorder.

The role of oxidative stress

Fibromyalgia is a chronic pain syndrome with unknown etiology and pathophysiology. Recent studies have shown some evidence demonstrating that oxidative stress may have a

role in the pathophysiology of fibromyalgia. It is unclear whether oxidative damage is the cause or just an effect of Fibromyalgia. Let us explore the various ways we are under attack both by normal metabolic processors to abnormal stressors such as Fibromyalgia. Low antioxidant status increases pain in fibromyalgia, which is often considered an oxidative stress disorder. Fibromyalgia dramatically increases oxidative attacks on your body, as the production of Oxyradicals exceeds your body's lowered capability to produce sufficient defenses to fight them, in turn causing further damage.

Antioxidants

Fibromyalgia is one of the most common chronic pain conditions. It is a disorder that causes musculoskeletal pain throughout the body. The pain causes tender joints in addition to fatigue and sleep, memory and mood abnormalities. For many, symptoms overlap and can become quite overwhelming. According to the National Fibromyalgia Association symptoms are found to occur in women more than in men, as 75-90% of those who have the condition are women. Symptoms can be the result of a physical trauma, surgery and infection or are due to severe psychological stress. In many cases however, symptoms gradually accumulate over time without a main trigger. Additional conditions include tension headaches, temporomandibular joint disorders, irritable bowel syndrome, anxiety and depression. Disturbances to light, sound and touch are also prevalent. The National Fibromyalgia Association suggests a diet plentiful in fruits and vegetables can be beneficial due to their phytonutrients that help reduce inflammation and ultimately pain. Consuming a raw diet rich in antioxidants, with uncooked fresh fruits and vegetables only increases the benefits as it may enhance the immune system’s ability to protect the body. In addition, healthy fats from avocado, olive oil and seeds are also essential. Omega 3-fatty acids can help reduce symptoms of pain specifically in the joints.

AIM AND OBJECTIVES

Though the above mentioned treatment profile is for fibromyalgia, antidepressants and NSAIDS are the more frequently used combination therapy for this disease. Keeping in view of the importance of this combination therapy for fibromyalgia, an effort is to be taken in this project work to evaluate the impact of CNS depressants on the potency of selected NSAIDS and so the impact of NSAIDS on the efficacy of CNS depressants in the treatment of fibromyalgia. The selected NSAIDS and CNS depressants for this study will be ibuprofen and diazepam respectively as these are frequently used prescription agents for fibromyalgia.

Plan of work

1. **Collection of the drugs**

- Ibuprofen
- Diazepam

2. **Collection of animals**

- Mice
- Rats

3. **Pharmacological experimentations**

- Effect of Diazepam and Ibuprofen on fibromyalgia disease using
- Effect of ibuprofen on the CNS depressant activity of diazepam
- Effect of diazepam on the analgesic activity of ibuprofen
- Effect of diazepam on the anti-inflammatory activity of ibuprofen
- Effect of ibuprofen on the ant anxiety activity of diazepam

4. **Mechanism study of the effect of both the drugs on their therapeutic potency by biochemical study.**

Experimental work

Materials

Drugs and Chemicals used

- Diazepam (DAP)
- Ibuprofen (IBP)
- Hydroden peroxide (H2O2)
- Potassium dihydrogen phosphate (PDP)
- Sodium dihydrogen phosphate (SDP)
- Methanol (MeoH)
- Acetylcholine (Ach)
- Potassium chloride (Pc)
- Sodium ion (Na)

Instruments used

- Digital balance (DB)
- Weight balance (WB)
- Ultraviolet spectroscopy (U.V.)

- Magnetic stirrer (MS)
- Eddy's Hot plate (EHP)
- Elevated plus maze (EPM)
- Swim test apparatus (SA)
- Thermometer (TM)

Experimental animals

The wistar strains of albino rats, weighing about 180-200g were used in the study. Animals were maintained under standard environmental conditions, *i.e* ambient temperature of 22±2ºC and at 45-55% relative humidity, 12 h each of dark and light cycle and fed with a standard pellet rats ad libitum. Water was supplied ad libitum. All the experiments were concluded in strict compliance according to ethical principles and guidelines provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (113\ac\CPCSEA\07). The study was approved by Institutional Animal Ethical Committee (NIET/IAEC\2011\24).

Collection of synthetic drugs

Synthetic drugs CNS depressants (Diazepam) and NAIDS (Ibuprofen) were collected from the college campus of Noida Institute of Engineering and Technology, Knowledge Park II, Greater Noida.

Experimental methodologies

Water avoidance stress

Fibromyalgia was induced by placing the animal (wistar albino rat) on the center of a clear plastic tank (45 cm x 25 cm) filled with water to a depth of 9 cm for a period of 1hr/day for 10 days.

Procedure

On the 14^{th} day, the fibromyalgia induced animals were used for the evaluation of the impact of diazepam on the effect of ibuprofen following the method of acetic acid induced writhing effect in rats. Whereas the impact of ibuprofen on diazepam was evaluated using elevated plus maze apparatus.

The fibromyalgia induced animals were used for the evaluation of the impact of diazepam and ibuprofen for which the animal was sacrificed and the gastrocnemius muscle tissue was isolated from the animal. The CRC of acetylcholine using the isolated gastrocnemius muscle

tissue was plotted in presence of diazepam and ibuprofen separately. In second muscle tissue preparation CRC was plotted in presence of ibuprofen. Third gastrocnemius muscle preparation was treated with ibuprofen and diazepam combination.

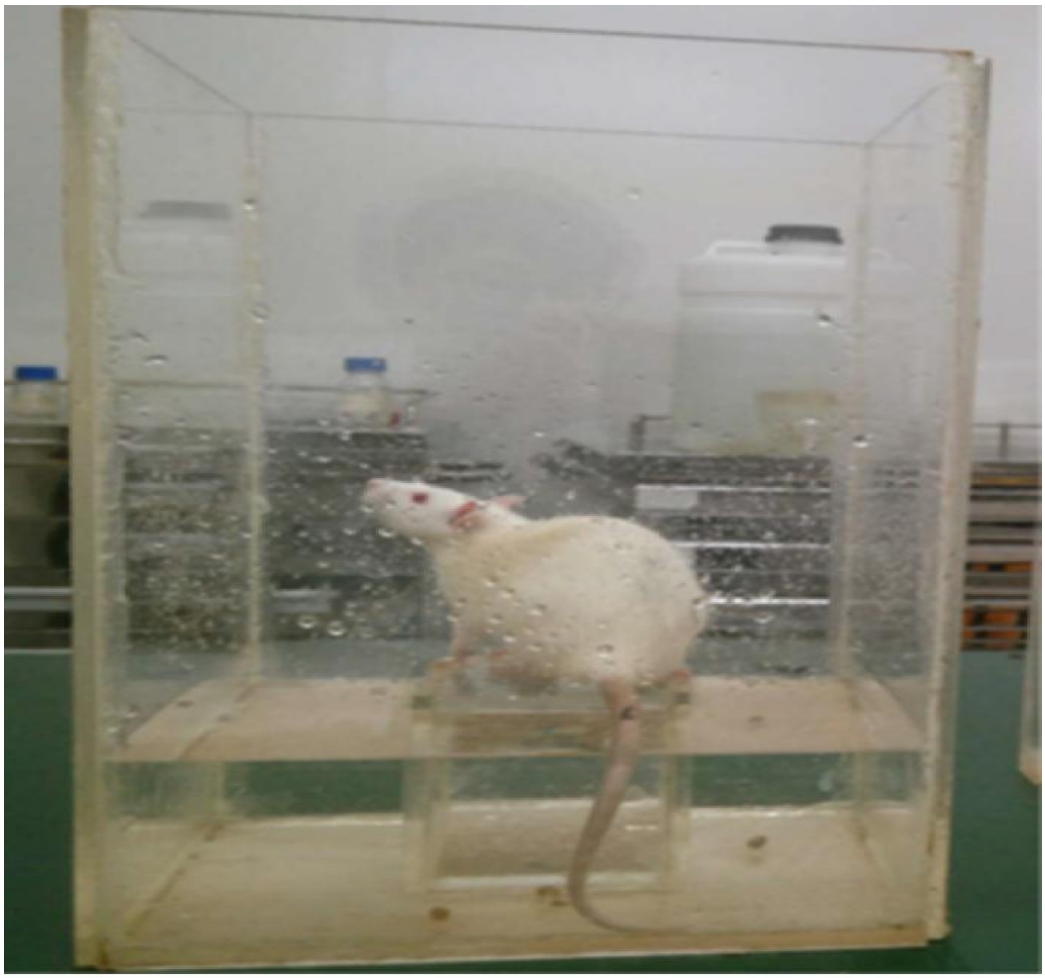

Figure no. 2: Water avoidance stress in rat.

Repeated cold stress model

The animal (Albino mice) exposed to cold stress develop several abnormal physiology such as a continuous lowering of blood pressure, sympathicotonic-type electrocardiogram, depression like behavior and hyperalgesia. In this model, mice are kept in a room temperature alternating between 24 and 4 °C. Every hour in the day time, and then kept at 4 °C over day. This procedure was repeated for 5days. This stress model to demonstrate its utility as a putative animal model for fibromyalgia. On day 1, the experiment starts with exposing mice to cold stress temperature (4°C) over day. From there, the temperature is then alternated between 24 and 4 °C every 30 minutes in the day time. This is repeated until morning on day 4. A nociception test is then conducted at room temperature at least 1h after the end of stress exposure.

Procedure

The animal (albino mice) put on hot plate apparatus before drug and checked the thermal stimulation (reduction in paw withdrawal latency in response to thermal stimulation). After that mice placed in hot plate apparatus with drug. In this method used CNS depressant (diazepam) and NSAIDS (ibuprofen) for checked the thermal hyperalgesia. On other hand mice loaded with cold stress show a shortened immobility time in the forced swim test, a test used to assess the anti-depressant effect of drug. Although prolonged immobility time is typically associated with depressant condition, the reduction immobility time may also indicate complex symptoms such as excessive emotion or anxiety- related depressant as immobility time recorded when the mice were given repeated injection of CNS depressant.

Figure no. 3: Repeated cold stress model in mice.

Figure no. 4: Repeated cold stress model in mice.

Antioxidant activity was performed by H2O2 method

Antioxidants play an important role in the prevention of human diseases. Antioxidant compounds may function as free radical scavengers, complexing agents for pro- oxidant metals, as well as reducing agents and quenchers of singlet oxygen formation. Antioxidants are often used in oils and fatty foods to retard their autoxidation. Therefore, the importance of the search for natural anti- oxidants has greatly increased in recent years. A focus is on natural-derived polyphenols because of their potential antioxidant and antimicrobial properties. Phenolic compounds exhibit considerable freeradical scavenging activity, which is determined by their reactivity as hydrogen- or electron- donating agents, their reactivity with other antioxidants and their metal chelating properties, as well as the stability of the resulting antioxidant-derived radicals. Hydrogen peroxide is reduced to hydroxyl radicals by the enzymes glutathione peroxidase and catalase in the presence of transition metals such iron or copper. The H_2O_2 radical is colorless. It is a discoloration assay, which is evaluated by the addition of the antioxidant to a H_2O_2 solution in ethanol or methanol and decrease in absorbance is measured at 230nm.

Procedure

The free radical scavenging activity was assayed spectrophotometrically (Blois, 1958) using Hydrogen peroxide (H_2O_2) radical. The radical scavenging activity can be followed by a loss of absorbance at 230 nm. Sample stock solutions (1mg/mL) were diluted to final concentrations of 50, 25, 12.5 and 6.25 mg/mL in methanol or DMSO. H_2O_2 solution was prepared using 1.2 mL H_2O_2 (0.2 mM in methanol), 3 mL methanol. H_2O_2 solution (0.45 mL) was added to 0.5 mL of sample solutions, shaken well by vortex, and allowed to react at room temperature.

The absorbance values were measured after 10 min at 230 nm by UV/Vis spectrophotometer. The free radical scavenging activity of samples was calculated according to the formula:

H_2O_2 radical scavenging activity (%) = [1-(Abssample - Absblank) / Abscontrol] x 100

Where Abssample is the absorbance of the experimental sample, Absblank is the absorbance of the blank; Abscontrol is the absorbance of the control. Each treatment was replicated thrice.

Statistical analysis

All results were expressed as mean ± SEM. The data were analyzed using analysis of paired t test and the group means were compared by Dunnett's test. Values were considered statistically significant with $P < 0.05$. Graph Pad Instant was used for the analysis of data.

RESULTS AND DISCUSSION

In the present study, it was observed that CNS depressant (Diazepam) potentiates the effect of NSAIDS (Ibuprofen) following the method of acetic acid induced writhing effect in rats (Table no-1). On the other hand ibuprofen causes increased effectiveness of diazepam was evaluated using elevated plus maze apparatus (Table no-2). On other hand it was found that isolated gastrocnemius muscle tissue with diazepam and ibuprofen causes' reduction in the contractile effect of acetylcholine. It was also observed that both the drugs relaxed the fibromyalgia induced gastrocnemius muscle tissue. Diazepam and ibuprofen relieves anxiety and inflammation respectively in fibromyalgia. Present study also showed their additional relaxing effect in fibromyalgia.

In the present study it found that hot plate apparatus (Table-3) before drug checked thermal stimulation response decreased and after drug thermal stimulation response increased effectiveness of both drug (diazepam, ibuprofen). On other hand swim test (Table 6.4) show a shortened immobility time in CNS depressant (like diazepam) and NSAIDS (like ibuprofen) drug.

Table no. 1: Effects of diazepam (4mg/kg) and Ibuprofen (100 mg/kg) on acetic acid induced writhing effect in fibromyalgia rats.

No. of Animals	Groups	No. of Writhing after (10min.)	Response (m ± sem)
6	Acetic acid control group	4.16±0.477	11.83±0.94
6	Diazepam	1.5±0.012	3.5±0.32
6	Ibuprofen	2.5±0.07	4.5±0.43

The values are expressed as mean ± SEM; n= 6 in each group. The data analyzed with paired t- test.

P>0.05 compared to normal controls, **P<0.01 compared control group to synthetic drug (diazepam and ibuprofen).

Table 2: Effects of diazepam (4mg/kg) and Ibuprofen (100 mg/kg) on the elevated plus maze in fibromyalgia rats.

Groups	No. of Animals	% Response of open Arm	Open Arm	
			No. of Entries (m ± sem) After 90 mins.	Av. Time (sec ± sem) on 14th days
Normal Control group	6	68%	2.5±0.23	3.83±0.6009
Diazepam	6	50%	1.7±0.106	7±0.730
Ibuprofen	6	58%	2.2±1.78	6.5±0.67

Values are mean ± SEM; n = 6 in each group. The data analyzed with paired t-test.

P>0.05 compared to normal controls, **P<0.01 compared control group to synthetic drug (diazepam and ibuprofen).

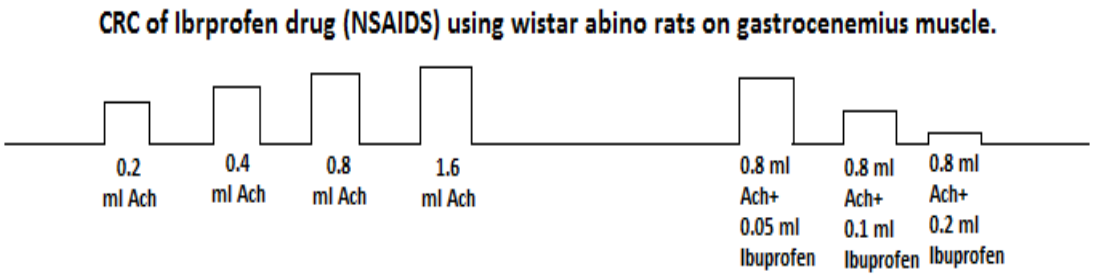

Figure no. 5: CRC of Ibuprofen drug using albino rats on Gastrocenemius muscle.

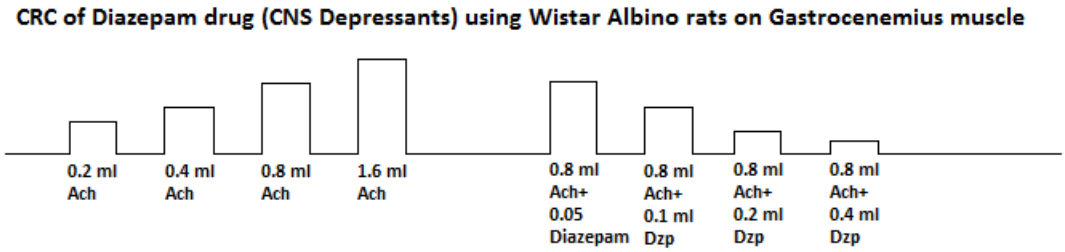

Figure no-6: CRC of Diazepam drug using albino rats on Gastrocenemius muscle.

Table no. 3: Effects of diazepam (4mg/kg) and Ibuprofen (100 mg/kg) on hot plate apparatus in fibromyalgia rats.

No. of Animals	Groups	Basal reaction time (sec.)		Reaction time After 60 min of drug Administration (m ± sem)	
		Paw Licking	Paw Withdrawal	PL	PJ
6	Normal Control	-	-	4.66±0.66	3.46±0.12
6	Diazepam	-	-	5.16±0.60	7.16±0.600
6	Ibuprofen	-	-	5.2±0.77	6.3±0.76

Values are mean ± SEM; n = 6 in each group. The data analyzed with paired t-test.

P<0.05 compared to normal controls, **P<0.01 compared control group to synthetic drug (diazepam and ibuprofen).

Table no. 4: Effects of diazepam (4mg/kg) and Ibuprofen (100 mg/kg) on Swim test in fibromyalgia rats.

No. of Animals	Group	Dose (mg/kg) I.P.	No. of Rotation/10 min. (m ± sem)
6	Normal control	-	4.33±0.7149
6	Diazepam	4	8.3±0.88
6	Ibuprofen	100	9.667±0.557

Values are mean ± SEM; n = 6 in each group. The data analyzed with paired t-test.

P<0.05 compared to normal controls, **P<0.01 compared control group to synthetic drug (diazepam and ibuprofen).

Antioxidant activity

The methanol extract showed strong antioxidant activity following H_2O_2 radical scavenging experiment. The CNS depressant (diazepam) and NSAIDS (ibuprofen) showed mild antioxidant activity following H2O2 radical scavenging experiment. H2O2 radical scavenging activity of showed CNS depressant 14±0.41 and scavenging activity of NSAIDS showed 8.23±0.39 absorbance at 230nm. The effect of antioxidants on H2O2 is thought to be due to their hydrogen donating ability. Though the H2O2 radical scavenging activity of ibuprofen was more than those of diazepam, the study showed that the ibuprofen and diazepam could serve as free radical inhibitors or scavengers.

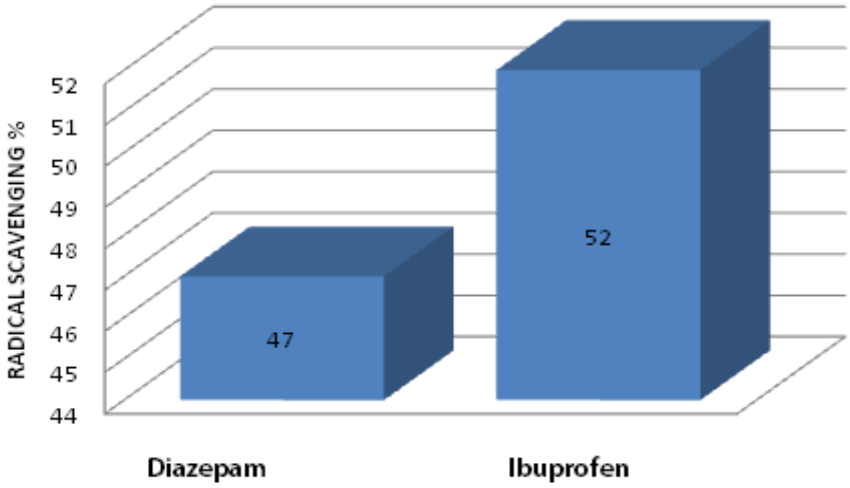

Figure no. 7: - H_2O_2 radical scavenging activity (%) by synthetic drugs (Diazepam and Ibuprofen) at 230nm.

CONCLUSION

Fibromyalgia is a complex, chronic, painful condition that can be characterized by a variety of nonspecific symptoms including palpable tender points; chronic, poorly defined, diffuse musculoskeletal pain; morning stiffness; fatigue, weakness; and sleep disturbance. 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.

Interventions aimed at reducing chronic symptoms for individuals with fibromyalgia must be a combination of education, psychological assistance and exercise, along with medications. There is no cure for fibromyalgia, but treatment aims to reduce symptoms and improve the quality of life. Both individuals with fibromyalgia and clinicians find the lack of standard and universally applicable successful treatments for fibromyalgia very frustrating. Therefore, finding the right combination of therapies, having a supportive social network and a strong sense of self-management are necessary for individuals with fibromyalgia to decrease the overall burden of disease.

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