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Fibromyalgia Syndrome –Newer Concepts in Pathogenesis Diagnosis, and Treatment

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ABSTRACT *Fibromyalgia syndrome is a chronic pain disorder. The pathogenesis of FMS is multifactorial.It includes central and peripheral pain mechanisms. With increasing knowledge on the pathophysiology newer treatment modalities are available which gives better quality of life for the patients. Treatment includes both pharmacological and non pharmacological therapy.*

KEYWORDS : fibromyalgia syndrome, Chronic pain disorder, treatment

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain disorder which is characterized by widespread aches and pains, sleep disturbances, fatigue along with a variety of symptoms including memory loss, psychological symptoms and depression[1].Fibromyalgia is more frequently seen in women with the ratio of 9:1. The prevalence is similar across the world and is about 1%- 2%. In this narrative review we have focused on the current understanding of pathogenesis of FMS along with its implication on the currently available therapies[2].

PATHOGENESIS OF FMS

Pathogenesis of FMS is multifactorial **(Figure 1**). Following factors in various combinations may be responsible in an individual patient.

Abnormality of pain perception and inhibition

There is reduced inhibition and abnormal processing of pain perception in patients with FMS. After perception of pain stimulus, the level of serotonin and nor-epinephrine released from peri-aqudectal gray matter, nucleus Raphae and descending inhibitory Magnus neurons, which inhibit nociceptive neurons, is low in patients with FMS[3]. Similarly high levels of substances P and excitatory amino acid neurotransmitters like glutamate and aspartate are found in patients with FMS, which cause abnormal pain processing, leading to spreading and increase in the intensity of pain[4]. The Low serotonin level in FMS is associated with altered sleep pattern and increased levels of substance P or associated with pain signalling, integration and modulation[5].

Central nervous system abnormality

Abnormality of central pain processing leads to central sensitization and reduced brain habituation, thereby lowering of pain threshold and leading to defective processing of nociceptive information in patients with FMS[6,7,8]. Role of central sensitization as the central mechanism for development of FMS however has not proven. In a recent study no evidence of excess pharmacological modulation via NMDA (N- methyl –d – aspartate) mechanism in FMS when compared to controls[9].

Conditioned pain modulation (CPM) which is a tonic inhibitory response leading to reduction in evoked pain by intense pain from a second source, is attenuated in patients with FMS.[8] Another phenomenon related to CPM in FMS is 'saturation effect' in which CPM cannot be further turned on by wide spread pain of FMS, which is the second source, if it is already turned on from an initial source of pain10.

Neuro-endocrine dysfunction

Primary neuro-endocrine dysfunction in FMS leads to disturbed Hypothalamo-Pitutary –Adrenal (HPA) axis function like relative adrenal hypo-responsiveness, low thyrotropin and growth hormone release[11,12,13]. Reduction in HPA axis activity leads to reduced level of corticotrophin-releasing hormone (CRH) secretion and reduced level of cortisole response which is thought to be the mechanism behind symptoms like fatigue, arthralgia, myalgia, disturbance of mood and sleep.[14,15] But in some patients with FMS, hyper activity of HPA axis and increased cortisone with blunted diurnal variation is also seen[15]. Suboptimal normal growth hormone secretion may contribute to impaired cognition, fatigue, muscle weakness and decreased exercise tolerance in FMS[16].

Defective sympathetic function is also seen in patients with FMS[17]. Similarly abnormal stress adaptation responses lead to stress related neuro-endocrine dysfunction and stress induced symptoms[18].

Psychological factors and psychiatric abnormalities

Various psycho-social factors like low educational status, unmarried status, low income status etc. are associated with higher chances of development of FMS[19]. Common psychiatric abnormalities associated with FMS include depression, dysthymia, panic disorder, simple phobia and somatoform disorder[20]. However, whether the psychiatric illness is due to chronic pain of FMS or FMS itself is a part of these psychiatric abnormalities remains unclear.

Sleep disorders

Unrefreshing and non-restorative sleep (NRS) is a common problem in FMS[21]. Other sleep disturbances include poor quality of sleep, early morning awakening and insomnia. Whether chronic pain of FMS leads to sleep disturbances or disturbance in sleep aggravates the symptoms of FMS is a controversial issue. But studies showed that disturbance in continuity of sleep impair pain-inhibitory mechanism contributing to the pathophysiology of chronic pain[22,23]. Sleep studies showed alpha-delta intrusion in electroencephalogram[24]. Fourth phase of sleep is most disturbed in FMS, so that the secretion of Growth hormone (GH) and Insulin like Growth Factor-1 (IGF-1) is deficient, leading to impairment of micro-trauma repair [25,26].

Genetic and Familial function

Genetic polymorphism of catechol-o-methyltransferse enzyme, Beta-adrenergic receptors gene, dopamine receptors gene and serotonin receptors gene are associated with FMS and other chronic pain syndromes[27,28,29,30]. Low gene expression for pro-inflammatory cytokine-4 and interleukin-10 are also associated with FMS[31]. There is a strong family association, in a study it was found that the first degree

relatives of FMS patient had 8.5 times higher risk of developing FMS compared to the general population[32].

Muscle micro-trauma.

Repeated muscle micro-trauma is believed to be a risk factor, and muscle biopsy showed various abnormalities including ragged-red fibers, inflammatory infiltrates, and moth-eaten fibers[33]. Prolonged muscle tension and ischemia also contribute to muscle micro trauma[34]. Changes in muscle pH due to ischemia sensitize various pain pathways[35]. In patients with FMS muscle phosphocreatine and ATP levels are low and the phosphodiesterase peaks are more frequent indicating sarcolemal membrane damage[36,37]. The level of various inflammatory markers , bradykinin, calcitonin, Gene-related peptide, substance P, TNFa, IL-1b, serotonin, and nor epinephrine are high in patients with myofascial pain, which sensitise nociceptors in muscle tissue and contribute to central sensitisation and chronic pain[38]. Muscle and tendon abnormalities, prolonged muscle tension and ischemia were thought to be significant in the pathophysiology of FMS earlier. But inability to explain systemic symptoms and absence of specific changes in muscle biopsy challenges this school of thought.

Peripheral pain triggers generation.

In FMS coexisting condition such as arthritis, bursitis, tendinitis etc act as peripheral pain generators and trigger more widespread pain[39].

Increased Brain-derived neurotrophic factor (BDNF) level has been reported in FMS, which appears to modulate pain hypersensitivity[40].

In FMS serum ferritin level has been found to be low, and the level of Magnesium and Zinc is also low[41]. Low magnesium level is associated with fatigue in FMS, where as low Zinc level shows association with tender points. Serum selenium level is usually normal[42] ..There is increase in interleukin levels especially IL -8 and increased oxidative stress.Reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide, increased lipid peroxidation, and increased autophagy and mitophagy are the various mitochondrial functional abnormalities seen in patients with FMS indicating increased oxidative stres[43,44]

In summary the two major hypothesis related to the pathogenesis of FMS are central neurochemical dysfunction hypothesis, where it is considered as predominant central neurological dysfunction and a peripheral dysfunction hypothesis, where the dysfunction is considered predominant of peripheral origin.

Even though there are various proposed pathological mechanism behind the development of FMS, the exact site of pathology, whether central or peripheral is not exactly known. The various factors associated with the risk of development of FMS can be divided in to (1) factors that predispose, (2) factors that precipitate the onset and (3) factors that perpetuate symptoms (**Table 1**)[45].

Diagnosis of FMS

Diagnosis of FMS is mainly clinical and examination will not reveal any major findings except for positive tender points; which may even be absent in 25% of cases of FMS[46]. ACR 1990 criteria for the Diagnosis of FMS depend of presence of widespread pain and demonstration of at least 11 positive tender points out of 18tender point. Pope and Hudson criteria for fibromyalgia include other features of FMS like fatigue Headache, sleep disturbance, neuropsychiatric complaints and irritable Bowel syndrome[47].The ACR 1990 criteria is questioned because of various limitations and the new ACR 2010 criteria helps the researchers to carry out large scale studies by eliminating the need for clinical examination (see table 2).

Table 2: Comparison of ACR 1990 Criteria and ACR 2010 Criteria

Drawback of 1990 ACR criteria[47]	Advantage of 2010 ACR criteria
A) Tender point demonstration. Examination rarely done properly Difficulty to quantity pressure applied. Time consuming B) Positive tender points Not a real measure of pain sensitivity. Depends on pain threshold Influenced by physiological stress. Exact cut off of II +ve tender points not known Tender points are not having any demonstrable Pathology. Increase in pain sensitivity can cause >18 TP positivity. 25% of FMS patients are negative for TP. Gives false impression that it is a musculoskeletal Disorder. C) Other co –morbid features of FMS not included in Diagnostic criteria.	1) No tender point demonstration. Easy Less time consuming. Modified self employed criteria replace physician examination. Can be used for large epidemiological survey. B) Other co – morbidities included in diagnostic criteria .

ACR 2010 criteria for FMS

The new ACR 2010 criteria for the diagnosis of FMS is not to replace the existing ACR 1990 criteria, but to help the researchers to carry out large scale studies by eliminating the need for clinical examination[48][- see table 3 and figure 2]. The ACR 2010 modified-self completed criteria, which include 19 site wide spread pain and self reported specific symptom, there by replaces the need for physicians estimation of specific symptoms score, helps in large epidemiological studies and postal surveys.

Table 2: 2010 ACR criteria for diagnosis of fibromyalgia 19 areas of widespread pain as per 2010 ACR criteria

fig 2

1

Diagnosis of FMS is mainly clinical and examination will not reveal any major findings except for positive tender points; which may even be absent in 25% of cases of FMS[46]. In this context it is important to recognise the numerous cognitive and somatic symptoms in FMS. Cognitive symptoms seen in FMS includes: (1) Working memory capacity impairment, (2) Recognition memory impairment, (3) Verbal knowledge impairment, (4) Anxiety and (5) Depression.Somatic symptoms that might be considered are: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Reynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Depending upon the clinical features FMS in divided in to 3groups, [see Table 4] which has got some prognostic implications also[49].

Table 3: Subgroups of FMS

Fibromyalgia can be primary or secondary, which is associated with other rheumatologic disease like Rheumatoid arthritis, Systemic Lupus Erythematosis and spondylo- arthropathy.

Several overlapping clinical syndrome, associated with abnormalities of pain perception, with overlapping clinical, epidemiological features are classified as central sensitivity syndrome and FMS belongs to one phenotype of this border family of conditions.

MANAGEMENT OF FMS

.treatment of chronic pain is challenging.it needs a multimodal approach which includes both pharmacological and non pharmacological modalities[50].

Non phramacological therapy
As per level of evidence in improvement of symptoms in patients with FMS, non-pharmacological therapy can be classified as shown below **(table 4).**

Cognitive behavioral therapy
It is a combination of behavioral and cognitive changes. It helps the patient to live with pain by changing the distressing thoughts and behavior associated with pain, which leads to emotions. Cognitive behavioral therapy has been found to be beneficial in reducing pain, negative mood and disability on follow up.[51]

Cardiovascular exercise
Aerobic exercise has been found to be beneficial in treatment of fibromyalgia by reducing the symptoms of fibromyalgia and improving the overall wellbeing of the patient. Randomized control studies have shown significant effect in reducing the number of tender points and also had a positive effect on depression[52] . Researchers have investigated the effectiveness of various exercises programs including bicycle ergometer, side step in the pool, jogging, walking outdoors and walking on a treadmill. Aquatic exercises are also found to be effective in FMS. [53]

Patient education
Patient education plays an important role in the treatment of patients with FMS. Educating the patient makes them to understand the symptoms and the nature of the disease thereby decreasing the dependence on medications, helping them to live with the disease and work efficiently.

Multidisciplinary approach
Exercise, cognitive-behavioral strategies and patient education commonly comprise the multidisciplinary approach. They are effective for decreasing pain and FMS impact and increasing self-efficacy and physical functioning.

Other non-pharmacological approaches
Strengthening exercise, acupuncture and hypnotherapy all help patient with FMS to get their pain relieved.

Cryotherapy is general use of low temperatures in medical therapy, which may decrease perception of symptomatic pain by stimulating the production of endorphins. Thus whole body cryotherapy may be used along with other treatment modalities in FMS to reduce the pain.[54,55]

Pharmacological therapy
There are more than 500 RCTS of different drugs in FMS are available. The commonly used drugs for the treatment of FMS includes Non selective Tricyclic antidepressants, Selective nor-adrenaline reuptake inhibitors, Opioids, Anticonvulsants, NSAIDs and Acetaminophen (**Table 5**).

Non selective tricyclic antidepressants
Most of the patients with FMS are depressed and antidepressants are useful in improving their quality of life. Amitryptilline is the most studied TCA in FMS. It reduces pain, fatigue and depressive symptoms in patients with FMS. But all the trials with TCA especially amitryptilline has a number of limitations. Most of the trials do not look in to the long term effects and they show improvement in symptoms at 6 weeks but they are not sustained after 3 months. g. They are started in the lowest possible dose and then titrated. Two meta-analyses have concluded that tricyclic antidepressants (amitriptyline, maprotiline, chlorimipramine, dothiepin) were better than placebo in the treatment of FMS. But there was no adjustment made for the use of rescue pain relief medications which might have affected the trial results56

Amitryptilline is absorbed from the gastrointestinal tract and is extensively metabolized by CYP2D6, CYP3A4, and CYP2C19-mediated N-demethylation into nortriptyline and is mostly excreted through kidneys. Weight gain is an important side effect. Anticholinergic side effects like constipation, xerostomia, cardiac conduction defects etc can be seen. These are the dose limiting side effects of TCA.

Selective noradrenaline reuptake inhibitors (SNRIs)
FMS is considered as a central sensitization syndrome. There is evidence that serotonine and noradrenaline may be involved in the enhanced CNS processing of painful stimuli by its effect on the central pain inhibitory mechanisms of the descending pain pathways. Medications that increase the concentration of serotonine and noradrenaline may alleviate the defects in neurotransmission and reduce the pain.

SNRI are potent dual reuptake inhibitors. s they have no much effect on adrenergic, cholinergic or histaminergic receptors. Hence they have less side effects compared to TCA which are non selective. SNRI mainly used in the treatment of fibromyalgia includes Duloxetin, Milnacipran and Venlafaxime .US Food And Drug Administration(FDA) approved Duloxetine in 2008 while milnacipran in 2009 for treatment of fibromyalgia. These drugs have been shown to improve pain significantly when compared to placebo.

Duloxetine inhibits serotonin and Nor-epinephrine reuptake in CNS and increases the availability of dopamine in prefrontal cortex. It is well absorbed when orally administered and the elimination half life is 12 hrs. It is metabolized by the liver and eliminated by kidneys. So hepatic function impairment may cause increase in the serum concentration of Duloxetine. But no dose adjustment is needed in patients with renal failure. Increased nor-adrenaline and serotonin availability in CNS and PNS will cause constipation, sweating, dry mouth and nausea. It may cause mild elevation in Blood pressure. But no QT prolongation was seen in ECGs[57,58].

There are 2 large RCT [59,60] comparing duloxetine to placebo in patients with FMS. The dosage of duloxetine used was 60mg QD to 60 mg BD. The trials were for 12 week period. Both trials showed that patients treated with duloxetine showed significant improvement in Brief Pain Inventory ,pain severity and interference scores, and other secondary outcomes, including the FIQ, Clinical Global Impression of Severity, and the Patient Global Impression of Improvement. The most important side effect noted was nausea. This could be reduced by staring in a lower dose of 20mg and titrating to the maximum tolerated dose slowly over a few weeks. Both depressed and non depressed persons responded equally to duloxetine.

Milnacipran is an SNRI similar to Duloxetine. The active metabolite of milnacipran is D-Milnacipran. Half life is 8-10hrs. It is metabolized by the liver and eliminated by the kidneys. Treatment with Milnacipran shows significant improvement in pain in patient with FMS.

In a large double blind placebo controlled trial[51] milnacipran was given as monotherapy to 125 patients in doses starting from 25mg/day to a max of 200mg/day. it was shown that patients receiving bd dosage of milnacipran showed significant reduction in weekly pain scores(50%)compared to those patients receiving once daily dosage. This shows that frequent dosing of the drug is needed to get adequate pain relief. It was also shown that more improvement was shown in non depressed patients with symptoms than in depressed patients.

Selective Serotonine Reuptake Inhibitors (SSRIs)
The important SSRIs are fluoxetine, sertraline, paroxetine and citalopram. The results of trials using SSRIs In FMS appear to be disappointing, probably due to absence of noradrenergic activity of the SSRIs[61,62]..

Anticonvulsants
Many anticonvulsants are effective in neuropathic pain. Anticonvulsants like gabapentin, lamotrigine and sodium valproate are effective in the treatment of fibromyalgia. The only FDA approved drug used in the treatment of fibromyalgia is pregabalin. Pregabalin acts by reducing the neuronal excitability. It binds to alpha 2 delta ligand and reduces calcium influx at nerve terminals and prevents the release of neurotransmitters.

Trials have shown that pregabalin significantly reduced sleep onset latency and no of awakenings which is a disturbing symptom in patients with FMS[54,55]. Pregabalin significantly increased the slow wave sleep. The first publish randomized control trial using pregabalin showed that it significantly improved pain and other symptoms in FMS like fatigue and disturbed sleep. Dosage of pregabalin used

in trials was up to 450mg/day. It is well absorbed orally, undergoes negligible metabolism in human body and mainly excreted through kidneys. Dizziness, nausea, euphoria, ataxia are the usual side effects. Pregabalin in patients with FMS showed significant improvement in pain, sleep, fatigue and quality of life compared to placebo[63,64].

Opioids

Pain pathways consist of ascending and descending pathways. The descending pathways modulate the transmission of pain in ascending pathways. The descending pathways have both opioids and non opioid pathways of which the opioids affect the opioid pathway. The opioid that has been used widely in FMS is tramadol. Tramadol is a novel analgesic with weak agonist activity at the mu opiate receptor combined with dual serotonin and norepinephrine reuptake inhibition that may exert anti-nociceptive effects within both the ascending and descending pain pathways. It is a synthetic opioid, which effectively control spontaneous pain in patients with FMS. It is usually started at a dose of 25-50mg/day and increased to a maximum of 200mg/day[65].

Even though there are 3 RCT [65,66,67] on the use of tramadol in FMS there is only one large trial which compares a combination therapy of tramdol with acetaminophen and placebo and it shows significant improvement in pain in the tramadol acetaminophen group .But continuous use of tramdol can cause significant dependence. Hence it should be cautiously used for pain control.

NSAIDs and Acetaminophen

NSAIDs [68]are mainly useful in peripheral pain and not very effective in central pain syndromes. Most of the patients with FMS have associated degenerative osteoarthritis or other conditions which will also aggravate the central pain and hence NSAIDs may be useful in reducing this peripheral pain.

Acetaminophen has effects on COX 1, 2, 3 receptors in brain and also on endocannabinoid system. So it is more preferred compared to NSAIDs and is commonly used in combination with opioids.

Tropisetron, a 5-hydroxytryptamine-3 receptor antagonist, and 5-hydroxytryptophan, , were shown to be more effective than placebo in RCTs. S-adenosylmethionine, an agent with both anti-inflammatory and antidepressant effects, was found helpful in one study 61 There has been no evidence that benzodiazepenes or non-benzodiazepene sedatives are effective in patients with FMS other than their role in sleep disturbances.[69]

CONCLUSION

Fibromyalgia is a widespread disorder characterized by widespread pain, sleep disturbances and psychological symptoms which is recognized as a part of central sensitization syndrome. Due to better understanding of the pathogensis of FMS, thereaputics are being constantly modified and the benefits of a multimodal approach are being recognized.

Conflicts of interests

None

Table 1: Factors associated with risk of development of FMS

Predisposing factors Genetic : polymorphisms in genes involved in systems regulating serotonin, dopamine, catecholamines, apolipoprotein. and β_2-adrenergic receptors Environmental : prebirth trauma, childhood physical or sexual abuse
Precipitating factors Injury from motor vehicle accidents, illness including autoimmune disorders, infections, surgical procedures, and psychological stressors.
Perpetuating factors Predisposing and precipitating events trigger processes resulting in persistent symptoms.

TABLE 2

2010 ACR criteria for diagnosis of FMS

1.Wide spread pain index (WPI)

Number of areas patient had pain over the past week (0-19 points).
The areas are neck, chest, abdomen, upper back, lower back and bilateral shoulder girdle, hip, jaw, upper arm, lower arm, upper leg, lower leg.

2.S.S scale
(a)Symptoms severity score: Fatigue, waking un-refreshed and cognitive symptoms; severity over the past week, using the following scoring (total score : 0-9)

0= No problem
1= Slight or mild problem, mild or inter militant.
2=moderate or considerable problem.
3=Severe pervasive, continuous, life disturbing problems.

(b) level of other somatic symptoms: considering the extent of somatic symptoms in general using the following score. (total score : 0-3)

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0= No symptoms
1=Few symptoms
2=moderate number of symptoms
3=great deal of symptom

2010 ACR criteria	**Score**
Wide spread pain index (WPI)	0-19
Symptoms severity over the past week	**(total score 0-9)**
Fatigue	0-3
Waking un-refreshed	0-3
Cognitive symptoms	0-3
Level of other somatic symptoms	(total score 0-3)
Extent of somatic symptoms	0-3

Total score is 0-31
WPI : 0-19
SSS : 0-12
Diagnosis of fibromyalgia

If patient satisfies the following three criteria :

WPI $\geq$7/19 and SS scale score $\geq$5 or WPI 3-6 and SS scale score $\geq$9

Symptoms present on a similar level for at least 3 months.

Patients do not have another disorder that would otherwise explain pain.

Modified Criteria
(1)WPI : 0-19
(2)SS scale score without extent of somatic symptom : total score 0-9
(3) Presence of abdominal pain, depression and headache in the past 6 months. (Yes =1, No= 0)

Modified criteria	Score
Wide spread pain index(WPI)	0-19
Symptoms severity over the past week	**(total score 0-9)**
Fatigue	0-3
Waking un-refreshed	0-3
Cognitive symptoms	0-3
Presence of associated symptoms	(total score 0-3)
Abdominal pain	No= 0, Yes =1
Headache	No= 0, Yes =1
Depression	No= 0, Yes =1

Total score is 0-31(WPI 19+ SSS without somatic symptoms 0-9 + Presence of abdominal pain, depression or headache 0-3)
Diagnosis of FMS
If total score is $\geq$ 13.

Table 3: Subgroups of FMS

Sub groups	Mood		Cognition		**Tenderness /hyperalgesia**	Response to treatment	Long term prognosis
Anxiety	Depression	Catastrophic behaviour	Ability to control pain				
1	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate
2	High	High	Marked	Poor	High	Poor	Poor
3	Little	Little	Very low	Good	Highest	Good	Good

Table 4: Non pharmacological therapy for FMS

Strong evidence
Cardiovascular exercise Cognitive behavioral therapy Patient education Multi disciplinary approach
Moderate evidence
Strengthening exercise Acupuncture Hypnotherapy
Little / No evidence
Cryotherapy Hypnosis

Table 5: Commonly used drugs in FMS

Drugs	Drug class	Level of Evidence*	Dose	Side effects
Amitriptyline	TCA	1A	10-50mg	Drowsiness, dry mouth, dizziness
Duloxetine	SNRI	1A	30-60mg	Nausea, headache, dizziness, insomnia
Milnacipran	SNRI	1A	25-200mg	Nausea, headache, dizziness, insomnia
Fluoxetine	SSRI	2A	20-60mg	Blurred vision , dry mouth, headache, increased sleep
Paroxetine	SSRI	2B	20 mg	Blurred vision , dry mouth, headache, increased sleep
Pregabalin	Anticonvulsant	1A	150-450mg	Dizziness, somnolence, weight gain, blurred vision
Gabapentin	Anticonvulsant	1 B	1200-2400mg	Dizziness, drowsiness, unsteadiness
Tramadol	Opioid	2B	50-300mg	Nausea, headache, dizziness, insomnia

* 1A : Systematic review of RCT, 1B : Individual RCT (with narrow confidence intervals), 2A : Systematic review of cohort studies, 2B : Individual review of cohort studies.

PATHOGENESIS OF FMS-figure 1

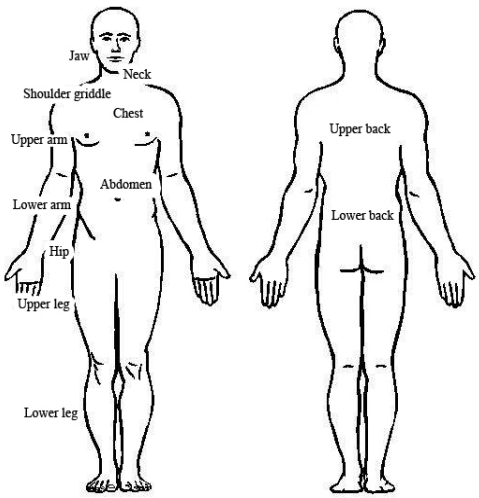

FIG 2-AREAS OF WIDE SPREAD PAIN AS PER 2010 ACR CRITERIA

1.. Neck 2. Chest 3. Abdomen 4. Upper back 5. Lower back 6 & 7.Shoulder griddle (Lt) & (Rt) 8 & 9. HIP (Lt) & (Rt) 10 & 11. Jaw (Rt) & (Lt) 12 & 13. Upper arm (Rt) & (Lt) 14 & 15. Lower arm (Rt) & (Lt) 16 & 17. Upper leg (Rt) & (Lt) 18 & 19. Lower leg (Rt) & (Lt).

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