Key Words: fibromyalgia, chronic pain, musculoskeletal pain, neuropathic pain, selective norepinephrine reuptake inhibitor, SNRI

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) for Treatment of Fibromyalgia: A Comprehensive Clinical Review

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ABSTRACT *~ Fibromyalgia is a complex clinical entity characterized by a broad range of symptoms including chronic widespread musculoskeletal pain, profound fatigue, impaired cognition, and mood disturbances. Current understanding of disease pathogenesis assumes neurotransmitter dysregulation and central pain sensitization play a key role resulting in heightened pain sensitivity. Genetic predisposition as well as alterations in endocrine and immune function have been implicated. Accurate diagnosis requires a comprehensive evaluation, and a personalized treatment approach is needed to address the biopsychosocial components of the disease process. Among pharmacologic treatment options, serotonin norepinephrine reuptake inhibitors (SNRIs) have demonstrated analgesic effects in addition to mood stabilizing properties. Currently, duloxetine and milnacipran are approved by the Food and Drug Administration although other agents in this drug class including venlafaxine and desvenlafaxine have been studied in the management of fibromyalgia. In addition, selective norepinephrine reuptake inhibitors, esreboxetine and reboxetine, as well as tramadol, a weak opioid mu-receptor agonist with SNRI activity have shown potential utility. Although some studies have demonstrated SNRIs to be effective and well tolerated in patients with fibromyalgia, individual response may vary. There remains a continued need for large scale clinical trials to establish the safety and clinical effectiveness of these agents in this patient population. Further information is needed to optimize patient selection and dosing regimens as well as elucidate the clinical factors associated with poor response. Moreover, pharmacologic agents may be combined with lifestyle changes and non-drug-based treatments to address the complex interactions of biological and psychosocial factors that facilitate disease development and persistence of symptoms.*
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Introduction

Fibromyalgia is a clinically challenging, and poorly understood disorder resulting from an intense interplay of biological, psychological and socio-environmental factors. Fibromyalgia is part of a group of disorders known as chronic overlapping pain conditions which are characterized by a state of pain amplification and a high rate of co-occurrence possibly secondary to shared neural mechanisms.[1] This group includes clinical entities such as chronic fatigue syndrome, temporomandibular disorders, irritable bowel syndrome, interstitial cystitis, and chronic pelvic pain.[1]

Fibromyalgia can be a debilitating condition, with care often complicated by diagnostic delays, clinical skepticism, and lack of a clear treatment paradigm. Optimal treatment requires a holistic, individualized approach inclusive of pharmacologic and non-pharmacologic interventions with the goal of improving overall functionality and quality of life. Among available pharmacotherapy, serotonin norepinephrine reuptake inhibitors (SNRIs) are regarded as the first line agents to reduce symptomology. Here, we provide an overview of the pathologic basis, diagnosis, and clinical management of fibromyalgia. The purpose of this narrative review is to provide clinicians with updated information pertaining to the use of SNRIs for fibromyalgia treatment. We summarize the current clinical evidence for each agent in this drug class regarding its clinical effectiveness, safety, and tolerability. In addition, we provide information regarding related drugs namely the selective norepinephrine reuptake inhibitors, esreboxetine and reboxetine, as well as tramadol, a weak opioid mu-receptor agonist with SNRI activity.

Disease Pathogenesis

The exact etiology of fibromyalgia has not been fully elucidated. Its pathophysiology is complex, influenced by a variety of genetic, environmental, neurologic, endocrine, and immunologic components. Previous studies suggest up to 50% of disease susceptibility may be attributable to genetic factors and several genes including SLC64A4, TRPV2, MYT1L, and NRXN3 have been implicated, although causation has not been well established.[2] Moreover, a gene-environment interaction has been theorized whereby environmental triggers such as physical trauma and psychosocial stressors are associated with epigenetic and phenotypical changes.[3] Impaired pain perception due to dysfunctional neurotransmitter systems has been recognized as a key pathogenic mechanism.[4] Reduced central nervous system levels of serotonin and noradrenaline have been found in fibromyalgia patients

potentially resulting in altered descending pain pathways and attenuated descending inhibition.[4] In addition, hyperactivity of glutamate in the insular cortex has been associated with lower pain thresholds. These neuro-transmitter alterations are postulated to contribute to fibromyalgia symptomology including mood and sleep disturbances as well as underlie central sensitization mechanisms whereby amplified central processing of pain signals results in hyperalgesia, allodynia, and widespread pain complaints. In addition, dysfunction of the autonomic and hypothalamic-pituitary axis stress systems may be induced by fibromyalgia risk factors such as early-life stress.[5] Immune system dysregulation may also occur and increased levels of inflammatory cytokines such as interleukin-6, interleukin-8, and TNF-alpha have been associated with nociceptor sensitization and development of hyperalgesia.[6]

Ultimately, fibromyalgia is a multifactorial disorder with a complex pathogenesis involving genetic predisposition, environmental influences, and a host of neurochemical, hormonal, and immune dysregulations. The interplay of these factors results in central sensitization, autonomic dysfunction, and immune-mediated pain modulation, ultimately manifesting as the hallmark symptoms of widespread pain, fatigue, and cognitive disturbances.

Clinical Evaluation & Diagnosis

Fibromyalgia has a reported prevalence of 2% to 8% in the United States.[7] Approximately 80% to 90% of cases affect women indicating a strong influence of hormonal, genetic, and psychosocial factors.[8–10] It is typically encountered in the 30–60 year age group, although the disease can present in childhood and adolescence, termed Juvenile Fibromyalgia Syndrome (JFMS).[11,12] Fibromyalgia may coexist with other chronic pain states such as systemic lupus erythematosus and rheumatoid arthritis, a phenomenon referred to as secondary fibromyalgia.[13]

Symptoms of fibromyalgia may fluctuate over time affecting different anatomic regions at different time points, and the clinical presentation can vary widely between affected individuals. A key clinical feature of fibromyalgia is chronic widespread musculoskeletal pain, and physical examination may reveal point tenderness at various body regions and generalized sensitivity to touch.[14] Musculoskeletal pain is often accompanied by a constellation of physical and mental symptoms including profound fatigue, insomnia, mood disturbance, and impaired cognition leading to diminished health-related quality of life.[15] A myriad of cognitive impairments including difficulties with attention, concentration, memory, and executive tasks, termed "fibrofog" are frequently encountered in fibromyalgia patients.[16] Fibromyalgia is associated with

a variety of psychiatric comorbidities including depression, anxiety, obsessive-compulsive personality, and post-traumatic stress disorder contributing to a worse clinical profile.[17] A bi-directional relationship between fibromyalgia and depression has been proposed, and pharmacological treatment with SNRIs can help improve both chronic pain and depression symptoms via independent mechanisms.[18]

Fibromyalgia is largely a clinical diagnosis, and obtaining a thorough clinical history and physical examination is paramount given its shared symptomatology with several other musculoskeletal, neurological, endocrinologic, and psychiatric disorders. Routine laboratory testing, imaging, and supplementary investigations such as polysomnography and electrodiagnosis may be pursued based on clinical suspicion of other disease states. The diagnostic criteria have evolved from an initial focus on presence of tender points to a more holistic and comprehensive evaluation. The 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria utilizes self-reported criteria namely the Widespread Pain Index (WPI), and the Symptom Severity (SS) Scale.[19] The WPI assesses pain experienced in 19 anatomical regions over the previous one week, with a score range of 0–19. The SS Scale, with score range of 0–12, includes assessment of fatigue, sleep disturbances, and cognitive difficulties. The diagnostic criteria are fulfilled by persistence of symptoms for three months or longer, absence of alternative diagnosis to explain the pain, and a WPI score of 3–6 and SS score ⩾9. A WPI score of ⩾7 and a SS score ⩾5 also meets the diagnostic criteria.

Overview of Treatment Options

Fibromyalgia is a symptomatically diverse condition, complicating treatment as one singular approach may not be successful for every patient. A wide array of non-pharmacologic and pharmacologic treatment options is available. The primary non-pharmacologic treatment involves implementing an exercise program focused on muscle strengthening, with aerobic exercises proving to be an effective approach for enhancing overall well-being and reducing pain severity.[20] Another promising category of exercise is mind-body centered practices such as yoga and tai chi. Exercise can be paired with other treatment modalities such as patient education programs and cognitive behavioral therapy (CBT). Educational programs aim to increase patient understanding of the interplay between behavior, neurobiological processes, and symptoms while dispelling negative associations surrounding fibromyalgia diagnosis. Research on its efficacy as a monotherapy is limited, however such courses may enhance outcomes when combined with a physical exercise program.[21–23] CBT seeks to modify negative thought patterns

to help patients avoid pain catastrophizing, a behavior associated with poorer clinical outcomes.[24,25] CBT also helps to reduce maladaptive behaviors, improve sleep hygiene, and decrease stress through relaxation techniques. Complementary and alternative interventions such as massage, chiropractic manipulation, acupuncture, and hydrotherapy may be trialed although their efficacy is poorly substantiated at this time.[23] A meta-analysis on acupuncture displayed no significant benefit on pain reduction compared to sham acupuncture.[26]

Currently, the pharmacologic agents pregabalin, duloxetine, and milnacipran are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia. Several classes of medications have been utilized to manage fibromyalgia symptoms including anti-epileptic drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, and SNRIs as well as muscle relaxants, dopaminergic agonists, and serotonin 5-HT3 receptor antagonists.[27] Oral cyclobenzaprine, a commonly utilized muscle relaxant, has demonstrated modest improvement in pain severity and sleep quality with no effect on fatigue or tender points.[28] A recent randomized, double-blind, placebo-controlled trial reported treatment with TNX-102 SL, a sublingual cyclobenzaprine formulation, resulted in significant reduction in daily pain from baseline at week 14 versus placebo ($P = 0.01$).[29] The medication was overall well tolerated with the most common adverse effects being oral hypoesthesia (17.3%), and oral paresthesia (5.6%) among 503 patients who received TNX-102 SL. Cannabinoids have also shown treatment benefits in multiple studies and may be useful for fibromyalgia patients with sleep disorders.[30,31] Sodium oxybate has shown pain reduction as well as improvements in fatigue, sleep, and functioning although it is associated with a high abuse potential.[32] Low dose naltrexone has been used off label for chronic inflammatory diseases, including fibromyalgia, however further studies are needed to establish its efficacy.[33] NMDA antagonists have also been trialed but a recent systematic review of memantine use in chronic pain found current evidence to be limited and uncertain.[34]

Serotonin and Norepinephrine Reuptake Inhibitors

SNRIs are a family of antidepressants with analgesic properties. Increased levels of serotonin and norepinephrine in the central nervous system are postulated to activate descending pain pathways and dampen nociceptive transmission at the level of the spinal cord.[35] Venlafaxine was the first SNRI to receive FDA approval in 1993 followed by duloxetine, desvenlafaxine, milnacipran, and levomilnacipran.[36] Each of these medications functions as a serotonin and norepinephrine reuptake inhibitor, with venlafaxine showing the strongest affinity for

serotonin reuptake inhibition at nearly a 30-fold ratio. In contrast, milnacipran demonstrates almost equal potency in inhibiting the reuptake of both neurotransmitters, while levomilnacipran exhibits a greater affinity for norepinephrine reuptake inhibition.[37,38] Whether the dominance of serotonin versus norepinephrine reuptake inhibition influences the clinical efficacy of each SNRI in the treatment of neuropathic pain has not yet been borne out by studies. While venlafaxine and duloxetine exhibit sequential manner of reuptake inhibition, first affecting serotonin and then norepinephrine, desvenlafaxine, milnacipran and levomilnacipran all have simultaneous blockade. The effect of the sequential mechanism of venlafaxine and duloxetine is seen in the side-effect profile, where serotonergic effects initially predominate, followed by noradrenergic effects. The pharmacokinetics of the individual medications including their metabolism and elimination are further described below.

Duloxetine

Duloxetine, a member of the nontricyclic SNRI category, acts by inhibiting serotonin and norepinephrine reuptake, and exhibits a 10-fold greater selectivity for serotonin reuptake inhibition.[39,40] With a half-life of approximately 12 hours, duloxetine is typically dosed once daily. The currently approved maximum dose is 60 mg/day; however, trials have demonstrated that doses up to 120 mg/day are also safe.[41] Elimination is primarily via the hepatic P-450 system, specifically 2D6 and 1A2 isoenzymes, and while its metabolism results in several metabolites, none have significant biologic activity.[42] In the United States, duloxetine has the highest number of FDA-approvals for an SNRI, treating both pain and psychiatric conditions including major depression, generalized anxiety, diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. The most commonly reported side effects include dry mouth, dizziness, constipation and sexual dysfunction.[43]

In the 2014–2017 PAIN-CONTRoLS Bayesian adaptive, open-label randomized controlled trial (RCT), 402 patients with cryptogenic sensory polyneuropathy were treated in a 1:1:1:1 ratio with duloxetine, nortriptyline, mexiletine or pregabalin. Among the drugs, similar efficacy rates of at least 50% pain reduction were achieved by duloxetine (23.0%), nortriptyline (25.4%), and mexiletine (20.3%). Pregabalin was determined to be the least efficacious, with only 15.1% achieving at least 50% pain reduction. Notably, duloxetine had the lowest discontinuation rate and a smaller proportion of participants reporting adverse effects compared to nortriptyline (46.8% versus 56.0%).

The most common reported adverse effects for duloxetine were nausea and insomnia.[44,45]

Milnacipran

Milnacipran is a SNRI which is metabolized in the liver and its inactive metabolites are eliminated renally in the urine.[46] It has a relatively short elimination half-life of approximately 6 to 8 hours.[46] According to a 2018 double-blind RCT, among 54 women with fibromyalgia, there was a nonsignificant difference in conditioned pain modulation between milnacipran and placebo ($P = 0.55$).[47] Alternatively, in a 15-week randomized, double-blind, placebo controlled trial published in 2009, 1196 patients with fibromyalgia were randomized to milnacipran 100 mg/day, milnacipran 200 mg/day or placebo. The milnacipran 100 mg/day and milnacipran 200 mg/day group showed significant improvements in pain after one week of treatment ($P = 0.004$ for both groups).[48] Notably, the most commonly reported side effects of milnacipran include nausea, headache, and constipation. These adverse effects led to early discontinuation of the study by 19.5% of participants in the 100 mg/day dosage group and 23.7% of participants in the 200 mg/day group, compared to only 9.5% in the placebo group. While milnacipran has shown potential in managing fibromyalgia symptoms, its long-term efficacy and feasibility as a treatment option for fibromyalgia-associated pain remain uncertain and require further investigation through extended trials and real-world application studies.

While milnacipran has demonstrated some efficacy in reducing fibromyalgia pain, particularly at doses of 100 mg/day and 200 mg/day, its clinical utility is tempered by the frequency of side effects, which contribute to a high discontinuation rate. The mixed findings in studies, including the lack of significant differences in certain outcomes such as conditioned pain modulation, highlight the need for more comprehensive research. Future studies should focus on elucidating milnacipran's long-term effectiveness, optimal dosing strategies, and its role in personalized treatment plans, particularly in light of the diverse symptomatology and patient responses characteristic of fibromyalgia.

Venlafaxine and Desvenlafaxine

Venlafaxine, a SNRI, is metabolized in the liver by the cytochrome P450 system with its metabolites primarily excreted in the urine.[49] The elimination half-life varies depending on the formulation: approximately 5 ± 2 hours for the immediate-release version, 6.8 ± 1.6 hours for the extended-release besylate formulation, and 10.7 ± 3.2 hours for the

TABLE 1

FDA-Approved and Off-Label SNRIs for the Treatment of Fibromyalgia

Medication	FDA Approval for Fibromyalgia	Dosage Range	Half-Life	Elimination Pathway	Mechanism of Action	Common Side Effects
Duloxetine	Yes	30–120 mg/day	~12 hours	Hepatic (CYP1A2, CYP2D6)	SNRI, serotonin-dominant	Nausea, insomnia, dizziness, dry mouth, constipation
Milnacipran	Yes	50–200 mg/day	~6–8 hours	Renal	SNRI, balanced serotonin and norepinephrine inhibition	Nausea, headache, constipation
Venlafaxine	No	75–375 mg/day	5–11 hours	Hepatic (CYP2D6), Renal	SNRI, serotonin-dominant	Hypertension, nausea, somnolence, anxiety
Desvenlafaxine	No	50–100 mg/day	~11 hours	Hepatic (CYP3A4), Renal	Active metabolite of venlafaxine, SNRI	Dizziness, hyperhidrosis, dry mouth
Levomilnacipran	No	20–120 mg/day	~12 hours	Hepatic (CYP3A4), Renal	SNRI, norepinephrine-dominant	Nausea, headache, insomnia

This table includes important details such as dosing ranges, half-life, elimination pathways, mechanisms of action, and common side effects for each medication. Among FDA-approved options, duloxetine and milnacipran are first-line treatments for fibromyalgia, while off-label agents such as venlafaxine, desvenlafaxine, and levomilnacipran may be considered based on clinical judgment.

extended-release hydrochloride formulation.[49] Desvenlafaxine is the principal active metabolite of venlafaxine.[50] Despite its pharmacologic potential, there is a limited number of RCTs evaluating the efficacy of venlafaxine and desvenlafaxine in the treatment of fibromyalgia. Two multicenter, randomized, placebo-controlled trials did not provide sufficient evidence for the effectiveness of desvenlafaxine in the treatment of fibromyalgia pain.[51] Male and female patients were randomized to a 27-week treatment with desvenlafaxine (50, 100, 200, or 400 mg/day) or placebo in the first study. The end point was a change from baseline in numeric rating scale pain score. After 12 weeks of treatment, none of the desvenlafaxine doses met the efficacy criteria and as such the study was discontinued. The second ended for business reasons prior to interim analysis. Common side effects of venlafaxine include exacerbation of depression, mania, or hypomania, along with dizziness, somnolence, anxiety, nausea, diarrhea, hypertension, hypercholesterolemia, and hyponatremia, further complicating its use in certain patient populations.[49]

A comprehensive list of FDA-approved and off-label serotonin-norepinephrine reuptake inhibitors (SNRIs) for the treatment of fibromyalgia, along with key clinical information, is provided in Table 1.

Eseboxetine and Reboxetine

Esreboxetine and reboxetine are highly selective norepinephrine reuptake inhibitors that have demonstrated some efficacy in alleviating fibromyalgia-related pain. Among the two, esreboxetine is recognized as being more potent and selective than its enantiomer, reboxetine. Both medications have been explored in the context of fibromyalgia treatment due to the involvement of both serotonergic and noradrenergic pathways in the mechanisms of pain signaling. Their targeted action on norepinephrine reuptake may play a role in modulating the central sensitization and pain amplification commonly observed in fibromyalgia. Reboxetine has been shown to cause fewer side effects such as dry mouth, constipation, nausea, diarrhea, and hypotension compared to other antidepressants. This is because it does not block alpha-1 receptors or 5-HT transporters and has a low affinity for muscarinic acetylcholine receptors.[52] Additionally, reboxetine has been found to be less sedating. Konuk et al. conducted a comparison between reboxetine and amitriptyline in fibromyalgia management.[53] The study compared the efficacy of the two drugs using the Fibromyalgia Impact Questionnaire (FIQ), Beck Depression and Anxiety Inventories, Hamilton Rating Scales for depression and anxiety as well as the Visual Analog Scale (VAS). Overall, both medications were found to result in improvements in

pain and depression scores with no statistically significant differences between both drugs. Arnold et al. studied the efficacy and safety of esreboxetine by conducting two separated placebo-controlled trials, with both showing significant improvement in the VAS scores at the 8-week and 14-week time points.[54,55] Similar trends were noted for the FIQ scores. Arnold et al. recently published data on the long-term safety and efficacy of esreboxetine, evaluating use over six months to one year.[56] While data continues to show improvement in FIQ and VAS scores, there was a 12.2% rate of discontinuations due to adverse effects of which dry mouth, constipation, nausea, and insomnia were most common. Overall, further studies examining the safety of these two newer agents in fibromyalgia treatment are needed as well as studies comparing them with currently approved medications.

Tramadol

Overall, the use of opioids in the treatment of fibromyalgia is generally discouraged. Research indicates that patients with fibromyalgia experience minimal anti-nociceptive effects from opioid therapy.[57] Tramadol, however, is a weak opioid mu-receptor agonist with SNRI activity as well as a N-Methyl-D-aspartate receptor antagonism.[58] Pereira da Rocha et al. assessed four existing RCTs that studied tramadol use in fibromyalgia.[59] Three studies examined the efficacy of tramadol in reducing pain severity while two studies assessed the efficacy of tramadol in improving quality of life.[60–63] Overall, tramadol has been found effective in reducing pain based on VAS score. However, studies indicate that tramadol alone did not show an improvement in the quality-of-life metric based on FIQ score. The most commonly reported adverse effects in these studies were nausea and headache, which may limit its tolerability for some patients. While evidence supports the association of tramadol with pain relief in fibromyalgia, it is insufficient to justify its use over established first-line pharmacological treatments. Additionally, there is a lack of comprehensive data regarding the long-term safety and potential risks of tramadol in managing fibromyalgia symptoms. Further studies are needed to better understand its role in fibromyalgia treatment, particularly in comparison to other therapeutic options.

A comprehensive list of emerging agents and alternative options with SNRI activity for the treatment of fibromyalgia, along with key clinical details, is provided in Table 2.

TABLE 2

Emerging Agents and Alternative Options with SNRI Activity for Fibromyalgia

Medication	Category	Dosage Range	Half-Life	Elimination Pathway	Proposed Utility in Fibromyalgia	Common Side Effects
Esreboxetine	Selective norepinephrine reuptake inhibitor	Not established	~6 hours	Renal	Modulates central sensitization	Dry mouth, constipation, insomnia
Reboxetine	Selective norepinephrine reuptake inhibitor	4–8 mg/day	~13 hours	Hepatic (CYP450)	Pain modulation via norepinephrine pathways	Dry mouth, nausea, low sedation
Tramadol	Weak opioid + SNRI activity	50–400 mg/day	5–7 hours	Hepatic (CYP2D6, CYP3A4), Renal	Pain relief, limited to short-term use	Nausea, dizziness, headache

This table includes important details for emerging and alternative medications with serotonin-norepinephrine reuptake inhibitor (SNRI) activity for the treatment of fibromyalgia. This table highlights selective norepinephrine reuptake inhibitors such as esreboxetine and reboxetine, as well as tramadol, which combines weak opioid activity with SNRI effects.

SNRI Monotherapy versus Combination Therapy

In the realm of fibromyalgia management, a single therapeutic approach may not always suffice to adequately address the multifaceted nature of symptoms. The use of SNRIs with other pharmacologic therapies for fibromyalgia has shown empirical beneficial evidence. Gilron et al. compared duloxetine-pregabalin combination to duloxetine alone, pregabalin alone, and placebo for six weeks in 39 patients.[64] The combination provided statistically significant improvement in pain intensity scores based on the Numeric Rating Scale compared to pregabalin monotherapy ($P < 0.05$); a statistically significant difference was not noted between the combination and duloxetine only groups. The combination group experienced greater improvement in FIQ score as well as quality of life score based on the 36-Item Short Form Survey compared to placebo, duloxetine alone, and pregabalin alone groups with differences reaching statistical significance ($P < 0.05$). Mease et al. reported similar outcomes with results favoring treatment with a milnacipran-pregabalin combination versus pregabalin alone in 364 patients over 12 weeks for pain reduction based on VAS (−20.77 versus −6.43; $P < 0.001$).[65] From a financial standpoint, a retrospective cohort study on healthcare costs and medication adherence by Marlow et al. further supports the use of combination therapies based on improved medication adherence and clinical outcomes despite increased costs.[66]

Other studies have countered or dampened the significant improvements reported with combination therapies. A study by Fattah et al. with 58 patients compared pregabalin in combination with milnacipran versus pregabalin alone for three months.[67] They found within both groups statistically significant improvements in VAS and FIQ scores ($P < 0.001$). However, there were no statistically significant differences between the two groups despite a greater numerical improvement in the milnacipran plus pregabalin group for pain, disease impact, and sleep pattern. They concluded the combination therapy did not demonstrate superiority over monotherapy. Another RCT compared 75 patients using pregabalin in combination with either amitriptyline, venlafaxine, or paroxetine for six months.[68] This study found at 24 weeks, the pregabalin with paroxetine provided greater improvement in Somatic Symptoms Scale-8 scores ($P < 0.002$), and depression scores ($P < 0.002$) compared to pregabalin in combination with either amitriptyline, or venlafaxine. In addition, at 24 weeks, the pregabalin with paroxetine group experienced higher medication tolerability ($P < 0.002$) as well greater improvements in life satisfaction ($P < 0.05$), elevated mood ($P < 0.05$), and sleep quality ($P < 0.05$) compared to pregabalin in combination with either amitriptyline, or venlafaxine.

Complementary and alternative treatments such as acupuncture, herbal medicine, mind-body techniques have been studied as an adjunct to pharmacological fibromyalgia management.[69] Bruti et al. completed an eight-week study with 31 patients comparing Okada Purifying Therapy (OPT) in combination with duloxetine versus duloxetine alone.[70] OPT is a holistic healing modality that combines Japanese natural medicine, energy work, and spiritual practices to cleanse and balance the body, mind, and spirit. These patients were randomized to the duloxetine only group or the duloxetine plus OPT group. Between the two groups only walking ability showed statistical improvement ($P = 0.002$) but not clinical significance. Milnacipran with CBT was compared to each monotherapy by Ang et al. in 58 patients over 21 weeks.[71] They found milnacipran-CBT combination demonstrated a two-fold reduction in pain intensity score ($P = 0.07$) and a three-fold improvement in physical function score based on the 36-Item Short Form Survey ($P = 0.09$) compared to milnacipran only. The milnacipran-CBT combination was also compared to CBT alone, with no statistically significant differences noted for the pain intensity score ($P = 0.44$) or the physical function score ($P = 0.77$).

Conclusion

Fibromyalgia is a complex and evolving chronic pain state associated with various somatic and psychological symptoms. It is postulated neural over sensitization and altered pain processing underlie this clinical entity, although the exact pathogenesis remains elusive. Its management demands a multifaceted approach including lifestyle modifications, non-pharmacological therapies, and pharmacologic management. The SNRIs duloxetine and milnacipran remain first-line treatment options, although pharmacotherapy for this condition continues to evolve with emerging new options in this drug class.

Available evidence is limited by studies with a small sample size and additional rigorous clinical trials are required to establish the clinical effectiveness, dosing, and long-term safety of these emerging agents. Future studies should also incorporate mood and quality of life metrics. Furthermore, future research should focus on uncovering the precise pathogenic mechanisms underlying this condition to facilitate the development of novel pharmacological therapies and enhance the available treatment options. ✤

Authorship Statement

All authors were involved in the study design, data interpretation, and preparation of the manuscript draft. All authors are accountable for all aspects of the work and approve the final manuscript.

Conflicts of Interests Statement

The authors have no conflicts of interests to report.

Abbreviations

CBT: cognitive behavioral therapy, FDA: Food and Drug Administration, FIQ: Fibromyalgia Impact Questionnaire, OPT: Okada Purifying Therapy, RCT: randomized controlled trial, SNRI: serotonin-norepinephrine reuptake inhibitor, VAS: Visual Analogue Scale.

References

1. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. *J Pain*. 2016;17(9):T93–T107. doi:10.1016/J.JPAIN.2016.06.002
2. D'Agnelli S, Arendt-Nielsen L, Gerra MC, et al. Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers. *Mol Pain*. 2019;15. doi:10.1177/1744806918819944
3. Park DJ, Lee SS. New insights into the genetics of fibromyalgia. *Korean J Intern Med*. 2017;32(6):984–995. doi:10.3904/KJIM.2016.207
4. Becker S, Schweinhardt P. Dysfunctional Neurotransmitter Systems in Fibromyalgia, Their Role in Central Stress Circuitry and Pharmacological Actions on These Systems. *Pain Res Treat*. 2011;2012:741746. doi:10.1155/2012/741746
5. Gyorfi M, Rupp A, Abd-Elsayed A. Fibromyalgia Pathophysiology. *Biomedicines*. 2022;10(12):3070. doi:10.3390/BIOMEDICINES10123070
6. O'Mahony LF, Srivastava A, Mehta P, Ciurtin C. Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. *Rheumatology (Oxford)*. 2021;60(6):2602. doi:10.1093/RHEUMATOLOGY/KEAB146
7. Arout CA, Sofuoglu M, Bastian LA, Rosenheck RA. Gender Differences in the Prevalence of Fibromyalgia and in Concomitant Medical and Psychiatric Disorders: A National Veterans Health Administration Study. *J Womens Health*. 2018;27(8):1035. doi:10.1089/JWH.2017.6622
8. Clauw DJ. Fibromyalgia: a clinical review. *JAMA*. 2014;311(15):1547–1555. doi:10.1001/JAMA.2014.3266
9. Ruschak I, Montesó-Curto P, Rosselló L, Aguilar Martín C, Sánchez-Montesó L, Toussaint L. Fibromyalgia Syndrome Pain in Men and Women: A Scoping Review. *Healthcare*. 2023;11(2). doi:10.3390/HEALTHCARE11020223
10. Yunus MB. The role of gender in fibromyalgia syndrome. *Curr Rheumatol Rep*. 2001;3(2):128–134. doi:10.1007/S11926-001-0008-3
11. Laurent R. Disorders of skeletal muscle. *The Musculoskeletal System: Systems of the Body Series*. Published online January 1, 2010:109–122. doi:10.1016/B978-0-7020-3377-3.00008-1
12. de Sanctis V, Abbasciano V, Soliman AT, et al. The juvenile fibromyalgia syndrome (JFMS): a poorly defined disorder. *Acta Bio Medica : Atenei Parmensis*. 2019;90(1):134. doi:10.23750/ABM.V90I1.8141
13. Clauw DJ. Fibromyalgia and related conditions. *Mayo Clin Proc*. 2015;90(5):680–692. doi:10.1016/J.MAYOCP.2015.03.014
14. Jahan F, Nanji K, Qidwai W, Qasim R. Fibromyalgia Syndrome: An Overview of Pathophysiology, Diagnosis and Management. *Oman Med J*. 2012;27(3):192. doi:10.5001/OMJ.2012.44
15. Borchers AT, Gershwin ME. Fibromyalgia: A Critical and Comprehensive Review. *Clin Rev Allergy Immunol*. 2015;49(2):100–151. doi:10.1007/S12016-015-8509-4
16. Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. *Rheumatol Int*. 2015;35(7):1115–1125. doi:10.1007/S00296-014-3208-7
17. Galvez-Sánchez CM, Duschek S, Del Paso GAR. Psychological impact of fibromyalgia: current perspectives. *Psychol Res Behav Manag*. 2019;12:117. doi:10.2147/PRBM.S178240
18. Yepez D, Grandes XA, Manjunatha RT, Habib S, Sangaraju SL. Fibromyalgia and Depression: A Literature Review of Their Shared Aspects. *Cureus*. 2022;14(5):e24909. doi:10.7759/CUREUS.24909

19. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62(5):600–610. doi:10.1002/ACR.20140
20. Sosa-Reina MD, Nunez-Nagy S, Gallego-Izquierdo T, Pecos-Martín D, Monserrat J, Álvarez-Mon M. Effectiveness of Therapeutic Exercise in Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Biomed Res Int*. 2017;2017. doi:10.1155/2017/2356346
21. Rooks DS, Gautam S, Romeling M, et al. Group exercise, education, and combination self-management in women with fibromyalgia: a randomized trial. *Arch Intern Med*. 2007;167(20): 2192–2200. doi:10.1001/ARCHINTE.167.20.2192
22. Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia. *J Rheumatol*. 1994;21(4):714–720. PMID: 8035399.
23. Hassett AL, Gevirtz RN. Nonpharmacologic Treatment for Fibromyalgia: Patient Education, Cognitive-Behavioral Therapy, Relaxation Techniques, and Complementary and Alternative Medicine. doi:10.1016/j.rdc.2009.05.003
24. Hassett AL, Cone JD, Patella SJ, Sigal LH. The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. *Arthritis Rheum*. 2000;43(11):2493–500. Accessed May 8, 2024. doi: 10.1002/1529-0131(200011)43:11<2493::AID-ANR17>3.0.CO;2-W. PMID: 11083273
25. Edwards RR, Bingham CO, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Rheum*. 2006;55(2):325–332. doi:10.1002/ART.21865
26. Cao H, Li X, Han M, Liu J. Acupoint stimulation for fibromyalgia: A systematic review of randomized controlled trials. *Evidence-based Complementary and Alternative Medicine*. 2013;2013. doi:10.1155/2013/362831
27. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia Pathogenesis and Treatment Options Update. *Curr Pain Headache Rep*. 2016;20(4):25. doi:10.1007/s11916-016-0556-x.
28. Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. *Arthritis Care Res (Hoboken)*. 2004;51(1):9–13. doi:10.1002/ART.20076
29. Lederman S, Arnold LM, Vaughn B, Kelley M, Sullivan GM. Efficacy and Safety of Sublingual Cyclobenzaprine for the Treatment of Fibromyalgia: Results From a Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care Res (Hoboken)*. 2023;75(11):2359–2368. doi:10.1002/ACR.25142/ABSTRACT
30. Berger AA, Keefe J, Winnick A, et al. Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):617–631. doi:10.1016/J.BPA.2020.08.010
31. Sagy I, Schleider LBL, Abu-Shakra M, Novack V. Safety and Efficacy of Medical Cannabis in Fibromyalgia. *Journal of Clinical Medicine*. 2019;8(6):807. doi:10.3390/JCM8060807
32. Russell IJ, Holman AJ, Swick TJ, Alvarez-Horine S, Wang YG, Guinta D. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: Results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain*. 2011;152(5):1007–1017. doi:10.1016/J.PAIN.2010.12.022
33. Patten DK, Schultz BG, Berlau DJ. The Safety and Efficacy of Low-Dose Naltrexone in the Management of Chronic Pain and Inflammation in Multiple Sclerosis, Fibromyalgia, Crohn's Disease, and Other Chronic Pain Disorders. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2018;38(3):382–389. doi:10.1002/PHAR.2086
34. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. *Eur J Pain*. 2019;23(7):1234–1250. doi:10.1002/EJP.1393
35. Robinson C, Dalal S, Chitneni A, et al. A Look at Commonly Utilized Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) in Chronic Pain. *Health Psychol Res*. 2022;10(2):32309. doi:10.52965/001C.32309
36. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: From monoamines to glutamate. *Exp Clin Psychopharmacol*. 2015;23(1):1. doi:10.1037/A0038550
37. Sansone RA, Sansone LA. Serotonin Norepinephrine Reuptake Inhibitors: A Pharmacological Comparison. *Innov Clin Neurosci*. 2014;11(3–4):37–42.
38. Stahl SM, Grady MM, Moret C, Briley M. SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectr*. 2005;10(9):732–747. doi:10.1017/S1092852900019726
39. Issa MA, Marshall Z, Wasan AD. Psychopharmacology for Pain Medicine. In: *Essentials of Pain Medicine*. 4th ed. 2018. doi:10.1016/B978-0-323-40196-8.00048-6.
40. Turcotte JE, Debonnel G, De Montigny C, Hébert C, Blier P. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacology*. 2001;24(5):511–521. doi:10.1016/S0893-133X(00)00220-7

41. Brummett C, Clauw DJ. Fibromyalgia and Centralized Pain States. In: *Essentials of Pain Medicine*. 4th ed. 2018:213–222.
42. Kuo F, Gillespie TA, Kulanthaivel P, et al. Synthesis and biological activity of some known and putative duloxetine metabolites. *Bioorg Med Chem Lett*. 2004;14(13):3481–3486. doi:10.1016/j.bmcl.2004.04.066
43. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. 2011;50(5):281–294. doi:10.2165/11539240-000000000-00000
44. Moisset X. Neuropathic pain: Evidence based recommendations. *Presse Med*. 2024;53(2):104232. doi:10.1016/j.lpm.2024.104232
45. Barohn RJ, Gajewski B, Pasnoor M, et al. Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS) Bayesian Adaptive Comparative Effectiveness Randomized Trial. Published online 2020. doi:10.1001/jamaneurol.2020.2590
46. Palmer RH, Periclou A, Banerjee P. Milnacipran: A Selective Serotonin and Norepinephrine Dual Reuptake Inhibitor for the Management of Fibromyalgia. *Ther Adv Musculoskelet Dis*. 2010;2(4):201. doi:10.1177/1759720X10372551
47. Pickering G, Macian N, Delage N, et al. Milnacipran poorly modulates pain in patients suffering from fibromyalgia: a randomized double-blind controlled study. *Drug Des Devel Ther*. 2018;12:2485–2496. doi:10.2147/DDDT.S162810
48. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther*. 2008;30(11):1988–2004. doi:10.1016/J.CLINTHERA.2008.11.009
49. Singh D, Saadabadi A. Venlafaxine. *xPharm: The Comprehensive Pharmacology Reference*. Published online February 26, 2024:1–5. doi:10.1016/B978-008055232-3.62846-6
50. Naseeruddin R, Rosani A, Marwaha R. Desvenlafaxine. *Indian J Psychiatry*. 2023;51(4):320–323. doi:10.4103/0019-5545.58303
51. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. *J Pain Res*. 2014;7:339–351. doi:10.2147/JPR.S55682
52. Krell HV, Leuchter AF, Cook IA, Abrams M. Evaluation of reboxetine, a noradrenergic antidepressant, for the treatment of fibromyalgia and chronic low back pain. *Psychosomatics*. 2005;46(5):379–384. doi:10.1176/APPI.PSY.46.5.379
53. Konuk N, Ortancil O, Bostanci B, Kiran S, Sapmaz P. A comparison of reboxetine and amitryptilline in the treatment of fibromyalgia syndrome with co-morbid depressive symptoms: An open-label preliminary study. *Klinik Psikofarmakoloji Bulteni*. 2010;20(1):29–37. doi:10.1080/10177833.2010.11790631
54. Arnold LM, Chatamra K, Hirsch I, Stoker M. Safety and efficacy of esreboxetine in patients with fibromyalgia: An 8-week, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2010;32(9):1618–1632. doi:10.1016/J.CLINTHERA.2010.08.003
55. Arnold LM, Hirsch I, Sanders P, Ellis A, Hughes B. Safety and efficacy of esreboxetine in patients with fibromyalgia: a fourteen-week, randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum*. 2012;64(7):2387–2397. doi:10.1002/ART.34390
56. Arnold LM, Mease PJ, Thomas Z, Moton A, Tabuteau H. Long-Term Safety and Efficacy of Esreboxetine for the Treatment of Fibromyalgia. *J Pain*. 2024;25(4):34. doi:10.1016/j.jpain.2024.01.161
57. Ngian GS, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. *Int J Rheum Dis*. 2011;14(1):6–11. doi:10.1111/J.1756-185X.2010.01567.X
58. Edinoff AN, Kaplan LA, Khan S, et al. Full Opioid Agonists and Tramadol: Pharmacological and Clinical Considerations. *Anesth Pain Med*. 2021;11(4):e119156. doi:10.5812/AAPM.119156
59. da Rocha AP, Mizzaci CC, Nunes Pinto ACP, da Silva Vieira AG, Civile V, Trevisani VFM. Tramadol for management of fibromyalgia pain and symptoms: Systematic review. *Int J Clin Pract*. 2020;74(3). doi:10.1111/IJCP.13455
60. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: A double-blind, randomized, placebo-controlled study. *American Journal of Medicine*. 2003;114(7):537–545. doi:10.1016/S0002-9343(03)00116-5
61. Qin L, Jiang F, Hu XQ. Effect of treating fibromyalgia syndrome with the combination of Tramadol and Amitriptyline. *Chinese journal of rural medicine and pharmacy [zhong guo xiang cun yi yao za zhi]*. 2009;16(3):18–19. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00793155/full
62. Russell J, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol*. 2000;6(5):250–257. doi:10.1097/00124743-200010000-00004
63. Biasi G, Manca S, Manganelli S, Marcolongo R. Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. *Int J Clin Pharmacol Res*. 1998;(1):13. Accessed November 30, 2024. https://thslc-houston.primo.exlibrisgroup.com/discovery/fulldisplay/cdi_pubmed_primary_9604730/01TEXASHEALTH_HOUSTON:TMC_INST

64. Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. *Pain*. 2016;157(7):1532–1540. doi:10.1097/j.pain.0000000000000558
65. Mease PJ, Farmer MV, Palmer RH, Gendreau RM, Trugman JM, Wang Y. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. *Ther Adv Musculoskelet Dis*. 2013;5(3):113–126. doi:10.1177/1759720X13483894
66. Marlow NM, Simpson KN, Vaughn IA, Jo A, Zoller JS, Short EB. Healthcare Costs and Medication Adherence Among Patients with Fibromyalgia: Combination Medication vs. Duloxetine, Milnacipran, Venlafaxine, and Pregabalin Initiators. *Pain Practice*. 2018;18(2):154–169. doi:10.1111/papr.12585
67. Abdel Fattah YH, Elnemr R. Efficacy of pregabalin as a monotherapy versus combined pregabalin and milnacipran in the management of fibromyalgia. *Int J Rheum Dis*. 2020;23(11):1474–1480. doi:10.1111/1756-185X.13953
68. Ramzy EA. Comparative Efficacy of Newer Antidepressants in Combination with Pregabalin for Fibromyalgia Syndrome: A Controlled, Randomized Study. *Pain Practice*. 2017;17(1):32–40. doi:10.1111/papr.12409
69. Saad M, Medeiros R. Complementary Therapies for Fibromyalgia Syndrome—A Rational Approach. *Curr Pain Headache Rep*. 2013;17(8):354. doi:10.1007/s11916-013-0354-7
70. Bruti G, Atencio MR, D'Urso A, Di Giacomo P, Di Paolo C. Okada Purifying Therapy in combination with duloxetine vs. duloxetine alone in patients with TMD and fibromyalgia: a randomized clinical study. *J Complement Integr Med*. 2021;18(2):371–377. doi:10.1515/jcim-2020-0116
71. Ang DC, Jensen MP, Steiner JL, Hilligoss J, Gracely RH, Saha C. Combining Cognitive-Behavioral Therapy and Milnacipran for Fibromyalgia. *Clin J Pain*. 2013;29(9):747–754. doi:10.1097/AJP.0b013e31827a784e