

Indication Review: Fibromyalgia

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End Date of Literature Search: 10/05/2018

Purpose for Review:

To evaluate safety and efficacy pharmacological treatments for fibromyalgia as requested by the Health Evidence Review Commission (HERC). Medical therapy for fibromyalgia is currently not funded by the Oregon Health Authority (OHA). The review focuses specifically on treatment of fibromyalgia as non-analgesics for treatment of chronic non-cancer pain or neuropathic pain have been reviewed previously.^{1,2} Evidence for tramadol in chronic non-cancer pain was also reviewed in 2017,³ and evidence for opioid analgesics was last reviewed in 2016.⁴

Research Questions:

1. What is the efficacy and safety of pharmacotherapy for treatment of fibromyalgia compared to placebo, other pharmacological therapies, or non-pharmacological treatments?
2. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) for which pharmacotherapy for fibromyalgia is more effective or associated with more long-term adverse effects?

Conclusions:

- There is no moderate or high strength evidence for any pharmacological treatment compared to placebo or other therapy. Like many other conditions for chronic pain, evidence supporting benefit of long-term pharmacological treatment for fibromyalgia is limited, efficacy of pharmacotherapy is relatively modest, and clinical trials often document a large placebo response upon evaluation of symptom improvement. Pharmacological interventions with the most evidence of benefit include duloxetine, milnacipran, and pregabalin, but applicability to a broader population is limited. In many trials, patients with comorbid medical conditions, particularly mental health conditions, were excluded. Similarly, many patients with a placebo response during run-in periods were excluded from trials. The strongest available evidence for efficacy outcomes for fibromyalgia drugs was of low strength meaning there is limited confidence that the estimated effects in the studies reflect the true effect, and further research is likely to change the estimated effect.
- There is low strength evidence that, compared to placebo, milnacipran or duloxetine may improve pain symptoms as evaluated by patient global impression of improvement or change (PGI-I or PGIC) of much or very much improved, 30% improvement in pain, pain intensity, and disability.⁵ Scores of much or very much improved and 30% improvement in pain typically correspond to an average 2 point improvement from baseline on a 0 to 10 numeric rating scale.⁶ The number needed to treat (NNT) for a minimal pain improvement with an average treatment duration of less than 3 months ranged from 5-10 depending on the outcome evaluated.⁵
- Milnacipran or duloxetine may have no clinical improvement for pain relief of 50% or more, sleep, fatigue, depression, cognitive disturbances, anxiety or quality of life (low strength of evidence). The NNT was 11 for pain relief of 50% or more (typically corresponding to a change of at least 3-4 points on a 0-10 rating scale), and while some other outcomes did achieve statistically significant differences from placebo, estimates were below the threshold for what would be considered a detectable clinically significant change.⁵

- There is low strength evidence that, compared to placebo, pregabalin may improve outcomes of pain relief of more than 50%, pain relief of more than 30%, and pain improvement as evaluated by a PGIC score of much or very much improved. The estimated NNT varied depending on dose and outcome, but ranged from 7 to 22.
- There is insufficient evidence on long-term use of pharmacological therapy for treatment of fibromyalgia, and it is unclear if modest improvements in pain outcomes would be sustained over time. The average duration of most trials was less than 3 months and few trials assessed outcomes beyond 6 months.
- Adverse effects more common with pregabalin compared to placebo included somnolence (number needed to harm [NNH] 7), dizziness (NNH 3), weight gain (NNH 18) and peripheral edema (NNH 19; low strength evidence). SNRIs (duloxetine, milnacipran and desvenlafaxine) were associated with an increased incidence of nausea (NNH 6) and somnolence (NNH 20).
- Evidence of benefit or harms for other pharmacological treatments (including tricyclic antidepressants, gabapentin, and tramadol) was insufficient. For example, while tricyclic antidepressants such as amitriptyline have historically been utilized for treatment of fibromyalgia, available evidence in randomized control trials has high risk of bias making estimates of the treatment effects uncertain.^{7,8} Overall, evidence for other pharmacological treatments was limited by significant risk of bias, small sample sizes, and/or limited applicability to patients with comorbid medical conditions.
- There is insufficient evidence to determine relative efficacy of pharmacological treatment compared to non-pharmacological therapies.
- Guidelines for fibromyalgia recommend patient education and focus primarily on nonpharmacological treatments such as exercise to improve symptoms of fibromyalgia. Pharmacotherapy and other non-pharmacotherapy options (e.g., cognitive behavioral therapy, multicomponent therapy, acupuncture, hydrotherapy, meditative movement, and mindfulness-based stress reduction) are recommended as second-line treatment options. Guidelines note that benefits of pharmacological treatments are relatively modest and, as magnitude of benefits are approximately equivalent to incidence of adverse effects from treatment, risks of therapy should be weighed against potential benefits.

Recommendations:

- No further research, review, or policy changes needed at this time.

Background:

Fibromyalgia is a chronic non-inflammatory pain disorder often associated with symptoms such as fatigue, depressed mood and cognitive dysfunction.⁹ Pain associated with fibromyalgia is typically widespread, diffuse, and may become progressively more persistent over time. Diagnosis is based primarily on history, physical exam, and absence of other disorders which would explain the chronic pain.⁹ The cause of fibromyalgia is unknown, but is thought to be related to abnormal pain processing in the nervous system and abnormal stress response in the hypothalamic pituitary adrenal axis. Estimated prevalence of fibromyalgia in North America is approximately 1-3% of patients and most commonly affects women. Risk factors which may be associated with increased incidence of fibromyalgia include physical trauma or injury, physical or sexual abuse, stress, infection, and sleep problems. Fibromyalgia is also commonly associated with a variety of comorbid conditions such as autoimmune disorders, psychiatric disorders, and functional somatic syndromes.

Goals of treatment include symptom improvement, functional improvement, enhanced patient self-management and self-efficacy, and management of comorbid conditions.⁹ Recommended therapy for treatment of fibromyalgia includes self-management strategies, non-pharmacological approaches as well as pharmacological treatment. Only 3 pharmacological agents are FDA-approved for treatment of fibromyalgia (**Table 1**). A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies. Other pharmacological agents which have been used off-label for treatment of

fibromyalgia include other pain medications such as opioids or acetaminophen, antidepressants such as amitriptyline or venlafaxine, other anticonvulsants such as gabapentin, and muscle relaxants like cyclobenzaprine.⁹

Table 1. Indications and Dosing for Drugs FDA-approved for Fibromyalgia¹⁰⁻¹²

Drug Name	Indication(s)	Strength/Route	Fibromyalgia Dose and Frequency
Duloxetine (Cymbalta® and generics)	<ul style="list-style-type: none"> • Fibromyalgia • Generalized anxiety disorder • Major depressive disorder (unipolar) • Musculoskeletal pain, chronic • Neuropathic pain associated with diabetes mellitus 	<ul style="list-style-type: none"> • 20, 30, 40, 60 mg ER capsules 	Initial: 30 mg once daily Max: 60 mg once daily
Milnacipran (Savella®)	<ul style="list-style-type: none"> • Fibromyalgia 	<ul style="list-style-type: none"> • 12.5, 25, 50 and 100 mg oral tablets 	Initial: 12.5 mg on day 1 titrated to 50 mg BID Max: 100 mg BID
Pregabalin (Lyrica®)	<ul style="list-style-type: none"> • Fibromyalgia • Neuropathic pain associated with diabetes mellitus • Neuropathic pain with spinal cord injury • Partial-onset seizures, adjunctive therapy • Postherpetic neuralgia 	<ul style="list-style-type: none"> • 25, 50, 75, 100, 150, 200, 225, 300 mg oral capsule • 20 mg/mL oral solution • 82.5, 165, 330 mg ER oral tablet 	Initial: 75 mg IR capsules BID Max: 225 mg IR capsules BID

Abbreviations: BID = twice daily; ER = extended release; IR = immediate release

Recently published guidelines from the European League Against Rheumatism (EULAR) focus on patient education and graded exercise as recommended first-line treatments to improve pain, sleep, function, and mood (strong recommendation).¹³ Second-line therapies include both pharmacological and non-pharmacological management and were based on weak recommendations.¹³ Second-line non-pharmacological therapies included cognitive behavioral therapy, multicomponent therapy, acupuncture, hydrotherapy, meditative movement, and mindfulness-based stress reduction which may be considered upon inadequate improvement to exercise.¹³ Recommendations for second-line pharmacological management included only low-dose amitriptyline, duloxetine, milnacipran, pregabalin, and cyclobenzaprine.¹³ Authors note that effect size for most pharmacological treatments is relatively modest, and the medications listed above are not licensed by the European Medical Agency for treatment of fibromyalgia because the small benefits did not outweigh risks associated with treatment.^{5,13,14} Canadian guidelines also include nonpharmacological therapies as a core modality of treatment with a focus on regular physical activity and incorporation of good coping mechanisms.¹⁵ Pharmacotherapy may be considered based on treatment response, but risks of therapy should be balanced against benefits.¹⁵ As with many other chronic pain conditions, efficacy of treatment with medications is relatively modest and should be weighed against the risks of therapy. For example, while pregabalin is FDA-indicated for multiple neuropathic conditions including fibromyalgia, it is also a controlled substance and may have some risk of dependence, abuse, or misuse.¹⁶

Many patient-reported scales are used to evaluate both functional improvement and pain severity in patients with chronic pain. Pain improvement is often evaluated using a variety of different symptoms scales in clinical trials. Common scales to assess pain symptoms include the Brief Pain inventory (BPI; range 0-10), numeric rating scales (range 0-10), visual analog scale (typically scale 0-10 or 0-100), fibromyalgia impact questionnaire (range 0-100), and patient global impression of improvement (range 1-7). Minimally clinically important differences for these scales can vary based on the condition and with acute versus chronic

pain, due to the subjective nature of these assessments, and there is no definitive definition of what may be considered a clinically important difference for an individual patient. However, consensus recommendations have been proposed for thresholds which may be considered clinically significant for patients with fibromyalgia or chronic pain. Generally, improvements of 20% on numeric rating scales have been considered of minimal benefit and changes of greater than 30% have been defined as moderate improvement in symptoms.⁶ Upon comparison of rating scales, a score of 2 on the PGI-I scale defined as being “much better” correlated with improvements of approximately 30% improvement from baseline or a 2 point improvement on the 11-point brief pain inventory.⁶ Similarly, a score of 1 on the PGI-I scale defined as “very much better” correlated with improvements of approximately 50% improvement in pain or a 3-4 point improvement on the 11-point brief pain inventory.^{6,17} Measurements for functional improvement include the Oswestry Disability Index (range 0-100), and the Roland-Morris Disability Questionnaire (range 0-24). Current literature for treatment of pain defines 10% of patients (corresponding to a NNT or NNH of 10) as a magnitude of benefit which might be considered clinically significant for a population of patients.⁵ However, estimates of clinical importance based on the magnitude of benefit for a population of patients are subjective and may vary depending on the risks and benefits for a particular patient.

In the OHP, mental health drugs including duloxetine and other antidepressants are carved-out and do not currently require prior authorization. Both milnacipran (Savella[®]) and pregabalin require PA to ensure medications are used for a funded diagnoses. Use of pregabalin for chronic neuropathic pain is also limited to patients who have intolerance, contraindications, or have tried and failed gabapentin therapy.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A Cochrane review evaluated efficacy of pregabalin compared to placebo for treatment of fibromyalgia.¹⁸ The review included 8 RCTs with 3283 patients.¹⁸ Three of the included studies had unclear randomization methods, 4 had unclear allocation concealment, 3 had unclear blinding methods, and 5 used last observation carried forward for missing data which may increase risk of bias and overestimate the effects of treatment.¹⁸ Only 2 studies involved more than 200 participants and only one study evaluated treatment for 6 months.¹⁸ Because the difference compared to placebo for most outcomes was relatively modest, these methodological limitations could have had a significant impact on the findings this review and may lead to overestimates of treatment effect. The majority of patients were women, white, age 47-50 years old, and with severe pain symptoms. For pain improvement of at least 50%, patients treated with pregabalin 300 mg (22% vs. 14%; NNT 14; RR 1.51, 95% CI 1.20 to 1.90), 450 mg (22% vs. 14%; NNT 9; RR 1.74, 95% CI 1.44 to 2.13), and 600 mg (24% vs. 15%; NNT 11; RR 1.64, 95% CI 1.28 to 2.10) had a statistically significant improvement compared to placebo.¹⁸ A 30% improvement in pain was also shown for 300 mg (39% vs. 28%; NNT 9; RR 1.4, 95% CI 1.2 to 1.6), 450mg (43% vs. 29%; NNT 7; RR 1.5, 95% CI 1.3 to 1.7), and 600 mg (39% vs. 28%; NNT 9; RR 1.4, 95% CI 1.2 to 1.6) compared to placebo. Similar results were noted with PGIC scores of much improved corresponding to an approximate 2 point improvement (36-40% vs. 27%; NNT 7-11) or very much improved corresponding to an approximate 3-4 point improvement (12-17% vs. 7-10%; NNT 12-22).¹⁸ Discontinuation due to lack of efficacy was

statistically more common with placebo (9-10%) than pregabalin 300-600 mg daily (2-4%; NNT 15-18), but discontinuation due to adverse events was more common with pregabalin 300-600 mg (16-28%) compared to placebo (9-11%; NNH 6-17) with a dose-related increase in discontinuations due to adverse events.¹⁸ Common adverse events which were statistically more frequent with pregabalin compared to placebo included somnolence (23% vs. 10%; NNH 7), dizziness (38% vs. 11%; NNH 3), weight gain (9% vs. 3%; NNH 18), and peripheral edema (8% vs. 2%; NNH 19).¹⁸ Two randomized discontinuation trials also evaluated maintenance of benefit in patients with an initial response to pregabalin. Of the 1492 patients given pregabalin, 34% of patients discontinued treatment during dose titration, and only 46% of patients (n=687) were enrolled in the study and had a 50% improvement in pain after 6 weeks of treatment.¹⁸ These patients were randomized to continue pregabalin treatment or transition to placebo. At 13 to 26 weeks after randomization, more patients given pregabalin had a 30% pain improvement from baseline compared to patients given placebo (40% vs. 20%; RR 1.9, 95% CI 1.5 to 2.4).¹⁸ However, only 14% of patients initially enrolled in the study completed the randomized phase of the trial with maintenance of therapeutic response (9.1% with pregabalin vs. 4.8% with placebo) indicating that only a very small proportion of patients may actually benefit from long-term treatment.¹⁸

A 2018 Cochrane review evaluated the efficacy and safety of SNRIs for treatment of fibromyalgia.⁵ The review included 7903 participants in 18 studies of duloxetine (n=7), milnacipran (n=9), and desvenlafaxine (n=1).⁵ Of the studies included, 7 were evaluated as having high methodological quality, 7 had moderate methodological quality, and 4 had low methodological quality.⁵ Only 2 studies evaluated treatment for longer than 6 months.⁵ Outcomes for which there was low quality evidence are reported in **Table 2**; no outcomes were evaluated with moderate or high quality evidence. Outcomes were downgraded due to risk of publication bias and indirectness.⁵ Other comparisons and outcomes were graded as very low or insufficient quality.⁵ For this systematic review, clinical significance was predefined as a NNT or NNH of 10 or less compared to placebo, or for continuous outcomes, a standardized mean difference (SMD) of greater than 0.2 corresponding to a small effect size.⁵ SDM allows comparison of results between trials that use different scales and metrics to evaluate similar outcomes (e.g., pain relief). Generally, effects of treatment were modest and pain relief of more than 30% or 50% (NNT of 10 and 11, respectively) was largely balanced with drug intolerability (NNH 14).⁵ An older 2015 Cochrane review evaluated efficacy of milnacipran alone compared to placebo, included many of the same milnacipran studies (n=6), and found similar magnitude of benefit and harms for outcomes of 50% pain improvement, 30% pain improvement, and treatment withdrawal due to adverse events.¹⁹

Table 2. Outcomes for which there was low strength of evidence compared to placebo. Outcomes evaluating symptom improvement were generally self-reported.⁵

Outcome	Interventions	Result	Authors Conclusions
Efficacy Outcomes			
Pain relief of ≥50%	Duloxetine, milnacipran	31% vs. 21%; ARR 0.09 (95% CI 0.07 to 0.11); NNT 11	No clinically meaningful benefit
PGI-I of much or very much improved	Duloxetine, milnacipran	51.9% vs. 29.3%; ARR 0.19 (95% CI 0.12 to 0.26); NNT 5	Clinically meaningful benefit
Pain relief ≥30%	Duloxetine, milnacipran	40.3% vs. 31.5%; ARR 0.10 (95% CI 0.08 to 0.12); NNT 10	Clinically meaningful benefit
Pain intensity	Desvenlafaxine, duloxetine, milnacipran	SMD -0.22 (95% CI -0.27 to -0.17)	Clinically meaningful benefit
Tenderness	Duloxetine, milnacipran	SMD -0.21 (95% CI -0.33 to -0.09)	Clinically meaningful benefit
Disability	Duloxetine, milnacipran	SMD -0.21 (95% CI -0.26 to -0.16)	Clinically meaningful benefit
Quality of life	Duloxetine, milnacipran	SMD -0.20 (95% CI -0.25 to -0.15)	No clinically meaningful benefit
Fatigue	Desvenlafaxine, duloxetine, milnacipran	SMD -0.13 (95% CI -0.18 to -0.08)	No clinically meaningful benefit
Depression	Duloxetine, milnacipran	SMD -0.16 (95% CI -0.21 to -0.11)	No clinically meaningful benefit

Cognitive disturbances	Duloxetine, milnacipran	SMD -0.16 (95% CI -0.21 to -0.10)	No clinically meaningful benefit
Discontinuation due to lack of benefit	Desvenlafaxine, duloxetine, milnacipran	6.5% vs. 9.1%; ARR -0.03 (95% CI -0.04 to -0.02); NNT 33	No clinically meaningful benefit
Sleep problems	Duloxetine, milnacipran	SMD -0.07 (95% CI -0.15 to 0.01)	No statistically significant benefit
Anxiety	Duloxetine, milnacipran	SMD -0.08 (95% CI -0.36 to 0.13)	No statistically significant benefit
Safety Outcomes			
Discontinuations due to AEs	Desvenlafaxine, duloxetine, milnacipran	19.1% vs. 10.2%; ARR 0.07 (95% CI 0.04 to 0.10); NNH 14	No clinically meaningful harm
Nausea	Desvenlafaxine, duloxetine, milnacipran	32.0% vs. 14.2%; ARR 0.16 (95% CI 0.14 to 0.19); NNH 6	Clinically meaningful harm
Somnolence	Duloxetine, milnacipran	10.9% vs 4.7%; ARR 0.05 (95% CI 0.02 to 0.08); NNH 20	No clinically meaningful harm
Insomnia	Desvenlafaxine, duloxetine, milnacipran	9.6% vs. 5.8%; ARR 0.03 (95% CI 0.01 to 0.04); NNH 33	No clinically meaningful harm

Abbreviations: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; NNH = number needed to harm; NNT = number needed to treat; PGI-I = patient global impression of improvement; SMD = standardized mean difference

A 2018 Cochrane review evaluated the efficacy and safety of mirtazapine for treatment of fibromyalgia based on an analysis of 3 RCTs (n=606).²⁰ No outcomes were evaluated as moderate or high quality due to high risk of bias for included studies, indirectness, imprecision, and risk for publication bias.²⁰ There was low quality evidence of no difference compared to placebo for the following outcomes: 50% pain improvement and discontinuation due to adverse events.²⁰ Pain improvement of at least 30% was more common with mirtazapine compared to placebo (risk difference [RD] 0.13, 95% CI 0.05 to 0.21; NNT 8; low quality evidence).²⁰ Similar improvements were noted with participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06, NNT 10; low quality evidence).²⁰ Adverse events which were more common with mirtazapine included somnolence (42% vs. 14%; RD 0.24, 95% CI 0.18 to 0.30; NNH 5; low quality evidence) and weight gain (19% vs. 1%; RD 0.17; 95% CI 0.11 to 0.23; NNH 6; low quality evidence).²⁰ Risks and benefits of therapy should be considered carefully as somnolence and weight gain were experienced frequently compared to the proportion of patients who achieved a moderate benefit from therapy.

A 2015 AHRQ systematic review examined the efficacy and safety of fibromyalgia treatments (pharmacological and non-pharmacological) in adult subgroups.⁹ The review included data from 34 RCTs and observational studies.⁹ All studies for pharmacological treatment had high risk of bias due to high attrition, reporting bias, small sample sizes, and source of funding.⁹ There was low strength of evidence of no difference in pain outcomes (PGI-I and BPI) with treatment of duloxetine in patients with depression or based on age compared to the general population.⁹ Similarly, there was no difference in PGI-I score with duloxetine treatment based on sex or race (low strength of evidence).⁹ Evidence for other outcomes or interventions of interest was of insufficient strength.⁹ Data were only available on short-term outcomes (3 months), and were limited by inconsistencies across studies and selective reporting of subgroup outcomes.⁹ For example, data on physical and social function were not commonly reported, and it is unclear if modest improvements in pain outcomes would be sustained over time.

A 2011 DERP systematic review evaluated direct comparative evidence for fibromyalgia treatments.²¹ Only 4 small RCTs were identified which compared amitriptyline to cyclobenzaprine, fluoxetine, nortriptyline, and immediate release paroxetine.²¹ There was no difference in any efficacy outcomes upon comparison of amitriptyline to cyclobenzaprine or nortriptyline (low strength evidence).²¹ Immediate release paroxetine 20 mg demonstrated a statistically significant improvement in pain (28% vs. 1%) and sleep problems (39% vs. 13%) compared to placebo over 6 weeks (low strength evidence based on 1 fair quality RCT of 68 patients).²¹ Evidence for the comparison of amitriptyline to fluoxetine was insufficient.²¹

Multiple systematic reviews, primarily Cochrane reviews, have been published assessing evidence for other pharmacotherapies for treatment of fibromyalgia. Pharmacotherapies studied include the following: monoamine oxidase inhibitors,²² selective serotonin reuptake inhibitors,²³ cannabinoids,²⁴ oral non-steroidal anti-inflammatory drugs,²⁵ antipsychotics,²⁶ amitriptyline,^{7,8} gabapentin,²⁷ topiramate,²⁸ lamotrigine,²⁹ oxycodone,³⁰ phenytoin,³¹ clonazepam,³² carbamazepine,³³ lacosamide,³⁴ valproic acid or valproate,³⁵ and antiepileptic drugs in children and adolescents.³⁶ An assessment of combination treatment for fibromyalgia included tramadol/acetaminophen, pregabalin/duloxetine, NSAIDs/benzodiazepines, amitriptyline/fluoxetine, amitriptyline/naproxen, amitriptyline/lidocaine, melatonin/antidepressant, carisoprodol/acetaminophen/caffeine, malic acid/magnesium, and MAOI/5-hydroxytryptophan.³⁷ Evidence from these reviews was generally of insufficient to very low quality for clinical outcomes of interest upon comparison to placebo or other therapies. Quality of evidence was limited by high or unclear risk of bias, limited population size, or small effect sizes. Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies are extremely uncertain.

After review, 13 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), or outcome studied (e.g., non-clinical).³⁸⁻⁵⁰

Guidelines:

No guidelines met quality inclusion criteria. After review, 2 guidelines were excluded due to lack of methodological documentation¹⁵ or conflicts of interest.¹³

Randomized Controlled Trials:

A total of 311 citations were manually reviewed from the initial literature search. Only trials reporting new evidence were considered for inclusion, and trials which offered no new additional information from sources already in the review were excluded. Citations were also excluded because of wrong study design (eg, observational, post-hoc analysis), comparator (eg, no control), outcome studied (eg, non-clinical). The remaining 10 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study/Design	Comparison	Population	Primary Outcome	Results
Allen, 2017 ⁵¹ MC, DB, PC RCT Duration: planned for 27 weeks; early study termination at 15 weeks N=697	1. Desvenlafaxine 50 mg 2. Desvenlafaxine 100mg 3. Desvenlafaxine 200 mg 4. Desvenlafaxine 400mg 5. Placebo	Adults with fibromyalgia and an average pain score ≥4 on the numeric rating scale (range 0-10) United States	Change from baseline in numeric rating scale pain score at study end (evaluated as a weekly mean score)	Change from baseline at week 15: 1. -2.09 points 2. -2.07 points 3. -2.24 points 4. -2.14 points 5. -2.21 points Early study termination due to lack of efficacy at week 15; treatment discontinuation: 68% of all patients, 28% due to early trial termination
Allen, 2017 ⁵¹	1. Desvenlafaxine 200 mg 2. Pregabalin 450 mg	Adults with fibromyalgia and an	Change from baseline in the	Change from baseline (mean, SE): 1. -1.60 (0.37)

<p>MC, DB, PC, parallel-group, RCT</p> <p>1 week placebo run-in period and patients with >30% reduction in pain were excluded from the double-blind treatment phase</p> <p>Duration: 8 weeks N=125</p>	<p>3. Placebo</p>	<p>average pain score ≥ 4 on the numeric rating scale</p> <p>United States</p>	<p>numeric rating scale pain score at study end (evaluated as a weekly mean score)</p>	<p>2. -1.70 (0.38) 3. -1.98 (0.37)</p> <p>Early study termination for business reasons; treatment discontinuation: 49% of all patients, 29% due to early trial termination</p>
<p>Ang, 2013⁵²</p> <p>DB, RCT N=58 Duration: 21 weeks</p>	<p>1. Milnacipran 100 mg + CBT 2. Milnacipran 100 mg + education 3. Placebo + CBT</p> <p>Treatments given in combination with other baseline pharmacotherapy but not with formal physical or exercise therapy</p>	<p>Adults with fibromyalgia and weekly average pain intensity score ≥ 4, on stable medication for ≥ 4 weeks.</p> <p>United States</p>	<p>Change from baseline in the weekly average pain intensity (range 0-10) and physical function (SF-36 physical function scale; range 0-100)</p>	<p>Pain intensity 1. -2.15 (0.43) 2. -0.97 (0.43) 3. -1.67 (0.45) 1 vs. 2: MD -1.18 (0.62), p=0.07 1 vs. 3: MD -0.49 (0.62), p=0.44 2 vs. 3: MD 0.69 (0.64), p=0.28</p> <p>Physical function 1. 13.47 (3.74) 2. 4.05 (3.84) 3. 15.04 (4.01) 1 vs. 2: MD 9.42 (5.48), p=0.09 1 vs. 3: MD -1.58 (5.50), p=0.77 2 vs. 3: MD 11.0 (5.66), p=0.06</p>
<p>Arnold, 2015⁵³</p> <p>DB, MC, PC, cross-over, RCT</p> <p>Duration: 2 blinded 6-week periods separated by a 2 week taper and washout period</p> <p>N=197 randomized (318 screened)</p>	<p>1. Pregabalin 150-450 mg titrated based on efficacy and tolerability 2. Placebo</p>	<p>Adults with fibromyalgia and a pain intensity score ≥ 4 and comorbid depression on stable SSRI or SNRI treatment</p> <p>Spain, Italy, Canada, United States</p>	<p>Weekly average pain intensity score (range 0-10) at end of treatment</p>	<p>Pain intensity at week 6 * 1. 4.84 (0.15) 2. 5.45 (0.16) MD -0.52 (95% CI -0.62 to -0.41); p<0.0001</p>
<p>Holman, 2005⁵⁴</p> <p>Single-center, DB, PC, RCT N=60</p>	<p>1. Pramipexole 4.5mg 2. Placebo</p>	<p>Adults >21 years with fibromyalgia and pain scores ≥ 5</p>	<p>Improvement in pain score (VAS, range 0-10) at 14 weeks</p>	<p>Mean change in pain score (SE) at week 14 1. -2.48 (0.38) 2. -0.71 (0.54) MD -1.77 (95% CI -3.07 to 0.47); p=0.008</p>

Duration: 14 weeks	Treatments given in combination with other baseline pharmacotherapy	United States		
Luciano, 2014 ⁵⁵ OL, RCT N=156 Duration: 6 months	<ol style="list-style-type: none"> 1. Acceptance and commitment therapy 2. Pregabalin 300-600mg + duloxetine 60-120mg with comorbid depression 3. No treatment (waitlist) 	<p>Adults with fibromyalgia</p> <p>Spain</p>	Fibromyalgia impact questionnaire (range 0-100)	<p>Mean change in the fibromyalgia impact questionnaire from baseline to 6 months</p> <ol style="list-style-type: none"> 1. -18.71 2. -3.85 3. 1.58
Martin, 2014 ⁵⁶ Single center, OL, RCT N=180 Duration: 6 months	<ol style="list-style-type: none"> 1. Psychological (CBT), medical, educational and psysiotherapeutic interventions twice weekly 2. Pharmacological treatment with amitriptyline (max 75mg), acetaminophen (max 4000 mg, and tramadol (max 400 mg) 	<p>Adults with fibromyalgia</p> <p>Spain</p>	Change in fibromyalgia impact questionnaire (range 0-100), pain in the last week, fatigue, anxiety, or coping mechanisms	<p>Mean fibromyalgia impact questionnaire at 6 months</p> <ol style="list-style-type: none"> 1. 70.33 (SD 16.48) 2. 76.81 (SD 14.18) <p>p=0.04</p> <p>No difference in other outcomes</p> <p>Attrition:</p> <ol style="list-style-type: none"> 1. 20 (22%) 2. 34 (37%)
Mease, 2013 ⁵⁷ OL, MC, RCT N=705 enrolled, 364 randomized, 264 completed study 4-12 week run-in period to evaluate response to pregabalin monotherapy; patients with incomplete response were randomized for 11 weeks	<ol style="list-style-type: none"> 1. Pregabalin 300-450 mg 2. Pregabalin 300-450 mg + milnacipran 100 mg 	<p>Fibromyalgia with pain score >40 (0-100 VAS scale)</p> <p>United States</p>	PGIC responder defined as much or very much improved (score of 1 or 2 on a scale of 1-7)	<p>PGIC response</p> <ol style="list-style-type: none"> 1. 20.8% 2. 46.4% <p>MD 25.6%; P<0.001</p>
Moldofsky, 2011 ⁵⁸ DB, MC, PC, phase 2, RCT N=36 Duration: 8 weeks	<ol style="list-style-type: none"> 1. Cyclobenzaprine 1 mg to 4 mg titrated based on tolerability 2. Placebo 	Adults with fibromyalgia and interrupted sleep for >50% of nights for 3 months before randomization	Fibromyalgia symptom improvement (use of LOCF for 7 patients who discontinued the study)	<p>Mean change in musculoskeletal pain (assessed with a 7 point scale a 10 body sites)</p> <ol style="list-style-type: none"> 1. -0.6 2. 0 <p>MD 0.6, p=0.044</p>

		Canada		<p>Mean change in HAD depression subscale (range 0-21)</p> <ol style="list-style-type: none"> -1.4 0.7 <p>MD 2.1; p=0.023</p> <p>No significant differences in fatigue or total HAD score</p>
<p>Olivan-Blazquez, 2014⁵⁹</p> <p>DB, PC, RCT</p> <p>N=63</p> <p>Duration: 6 months</p>	<ol style="list-style-type: none"> Memantine 20 mg Placebo 	<p>Adults with fibromyalgia</p> <p>Spain</p>	<p>Pain Improvement by VAS (range 0-10)</p>	<p>Mean (SD) VAS at 6 months (with imputation using LOCF for 17% of patients who discontinued the study)</p> <ol style="list-style-type: none"> 4.87 (1.45) 7.01 (1.53) <p>MD 2.14; p=0.001</p>
<p>Ramzy, 2017⁶⁰</p> <p>Single-center, RCT</p> <p>N=75</p> <p>Duration: 6 months</p>	<ol style="list-style-type: none"> Amitriptyline 25 mg daily Venlafaxine 75 mg daily Paroxetine 25 mg daily <p>Given in combination with pregabalin 75 mg daily</p>	<p>Adults with fibromyalgia</p> <p>Egypt</p>	<p>Somatic Symptoms Scale-8 (range 0-32)</p>	<p>Somatic Symptoms Scale-8 at 6 months (median, range)</p> <ol style="list-style-type: none"> 7 (0-14) 8 (8-8) 6 (4-13) <p>1 vs. 3: p<0.05 2 vs. 3: p<0.02</p>
<p>Russell, 2000⁶¹</p> <p>MC, DB, PC, discontinuation, RCT</p> <p>N=100 enrolled, 69 randomized</p> <p>Duration: 9 weeks</p> <p>All patients given open-label tramadol for 3 weeks and then patients with treatment benefit were blinded and randomized to placebo or tramadol for 6 weeks</p>	<ol style="list-style-type: none"> Tramadol (50-400 mg daily titrated based on tolerability during open-label phase) Placebo 	<p>Adults with fibromyalgia</p> <p>United States</p>	<p>Time to treatment discontinuation due to inadequate pain relief</p>	<p>Time to treatment discontinuation graphically reported ; p=0.001</p> <p>Proportion of patients who maintained treatment at 6 weeks</p> <ol style="list-style-type: none"> 20 (57.1% of randomized patients; 20% of enrolled patients) 9 (27% of randomized patients; 9% of enrolled patients) <p>MD 30.1%; p=0.015</p> <p>Discontinuation due to adverse events (primarily nausea, vomiting, dizziness): n= 20 (20% of enrolled patients receiving tramadol)</p>

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; DB = double blind; HAD = hospital anxiety and depression scale; LOCF = last observation carried forward; MC = multicenter; MD = mean difference; OL = open label; PC = placebo-controlled; PGIC = patient global impression of change scale; RCT = randomized clinical trial; SC = single-center; SD = standard deviation; SE = standard error; VAS = visual analog scale.

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Appendix 1: Specific Drug Information for FDA-approved drugs

Table A1. Clinical Pharmacology and Pharmacokinetics.¹⁰⁻¹²

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Duloxetine	Serotonin and norepinephrine reuptake inhibitor	Well absorbed	Hepatic metabolism via CYP1A2 and CYP2D6 Excreted in urine (70%) and feces (20%)	<ul style="list-style-type: none"> • Half-life: 12 hours • Cmax: 6 hours • Vd: 1640 L (>90% protein binding)
Milnacipran	Serotonin and norepinephrine reuptake inhibitor	Well absorbed Bioavailability 85-90%	Hepatic metabolism Urinary excretion (50% as unchanged drug)	<ul style="list-style-type: none"> • Half-life: 6-8 hours • Cmax: 2-4 hours • Vd: 400 L (13% protein binding)
Pregabalin	Binds voltage-gated calcium channels, modulates calcium influx in nerves, and inhibits neurotransmitter release including glutamate, norepinephrine, serotonin, dopamine, substance P, and calcitonin gene-related peptide	Bioavailability 90%	Excreted unchanged in urine (90%)	<ul style="list-style-type: none"> • Half-life: 6 hours for adults • Cmax: ER 8 hours, IR 3 hours • Vd: 0.5 L/kg (0% protein binding)

Use in Specific Populations:

Duloxetine:⁶²

Pregnancy: Based on animal data, may cause fetal harm.

Lactation: Exercise caution when administering to a nursing woman.

Hepatic impairment: Avoid use in patients with chronic liver disease or cirrhosis.

Renal impairment: Avoid use in patients with severe renal impairment (eGFR <30 mL/min).

Geriatric use: Falls and clinically significant hyponatremia have been reported. No dose adjustment recommended based on age.

Smoking Status: Bioavailability of duloxetine is reduced with concomitant smoking, but dose adjustments are not recommended.

Milnacipran:⁶³

Pregnancy: Based on animal data, may cause fetal harm.

Lactation: Milnacipran is present in milk, and there is limited data regarding infant exposure. Use caution if administered while breastfeeding.

Hepatic impairment: Avoid use in patients with chronic liver disease or cirrhosis.

Renal impairment: Used with caution in patients with moderate renal impairment.

Geriatric use: Clinically significant hyponatremia have been reported in elderly patients; consider discontinuation if present.

Pediatric use: Safety and effectiveness in pediatric patients with fibromyalgia has not been established. Use in pediatric patients is not recommended.

Pregabalin:¹⁶

Pregnancy: May cause fetal harm. Advise of potential risks to the fetus.

Lactation: Breastfeeding is not recommended due to potential risk of tumorigenicity.

Renal impairment: Dose adjustment recommended for those with renal impairment.

Pediatric use: Safety and effectiveness in pediatric patients with fibromyalgia has not been established.

Drug Safety:

Boxed Warnings:^{62,63}

- Duloxetine: Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.
- Milnacipran (Savella®): Increased risk of suicidal ideation, thinking, and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Savella® is not approved for use in pediatric patients.

Contraindications:

- Duloxetine and milnacipran– Serotonin syndrome and monoamine oxidase inhibitors.^{62,63}
Do not use MAOIs intended to treat psychiatric disorders with duloxetine or within 5 days of stopping treatment with duloxetine. Do not use duloxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start duloxetine in a patient who is being treated with linezolid or intravenous methylene blue.
- Pregabalin – Known hypersensitivity to pregabalin.¹⁶

Table A2. Summary of Warnings and Precautions.^{16,62,63}

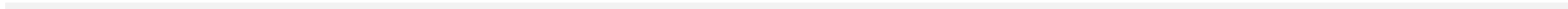
Warning/Precaution	Duloxetine	Milnacipran	Pregabalin
Suicidal thoughts/risk	X	X	X
Seizures	X	X	X
Serotonin syndrome	X	X	
Hepatotoxicity	X	X	
Abnormal bleeding	X	X	
Withdrawal symptoms upon discontinuation	X	X	
Urinary hesitation and retention	X	X	
Increased blood pressure and heart rate	X	X	
Orthostatic Hypotension, falls and syncope	X		
Dizziness and somnolence			X
Activation of mania or hypomania	X	X	
Angle-closure glaucoma	X	X	
Hyponatremia	X	X	
Drug interactions with inhibitors of CYP1A2 and thioridazine	X		
Worsening glucose control in diabetes	X		

Conditions that slow gastric emptying	X		
Severe skin reactions	X		
Peripheral edema			X
Hypersensitivity reactions and angioedema			X
Weight gain			X
Tumorigenic potential			X
Ophthalmologic effects			X
Creatine Kinase Elevations			X
Decreased platelet count			X
PR interval prolongation			X

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to October Week 1 2018

1	exp Analgesics, Opioid/	105716
2	exp Anti-Inflammatory Agents, Non-Steroidal/	186834
3	exp Antidepressive Agents/	136270
4	exp Anticonvulsants/	132011
5	gabapentin.mp.	5351
6	topiramate.mp.	4007
7	lacosamide.mp.	582
8	exp Benzodiazepines/	63145
9	exp Cannabinoids/	12538
10	nabilone.mp.	265
11	exp Amantadine/	5626
12	milnacipran.mp.	596
13	pramipexole.mp.	1245
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	593078
15	exp Fibromyalgia/	7773
16	14 and 15	868
17	limit 16 to (english language and humans)	736
18	limit 17 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	311



Appendix 3. Abstracts of randomized controlled trials

1. Allen R, Sharma U, Barlas S. Clinical Experience With Desvenlafaxine in Treatment of Patients With Fibromyalgia Syndrome. *Clinical pharmacology in drug development*. 2017;6(3):224-233.
Two multicenter, randomized, placebo-controlled, adaptive-design trials of desvenlafaxine for fibromyalgia syndrome (FMS) were conducted. In study 1, male and female patients were randomized to a 27-week treatment with placebo or desvenlafaxine 50, 100, 200, or 400 mg/d. In study 2, female patients were randomized to an 8-week treatment with placebo, desvenlafaxine 200 mg/d, or pregabalin 450 mg/d after a placebo run-in. The primary efficacy end point was change from baseline in numeric rating scale (NRS) pain score. Protocol-specified interim analyses were planned after 12 (study 1) and 8 (study 2) weeks of treatment. Safety data were collected. In all, 697 patients were randomly assigned to treatment in study 1. At the interim analysis (n = 346), none of the desvenlafaxine doses met the efficacy criteria (mean [SE] advantage over placebo, -0.21 [0.36] to 0.04 [0.35]), and the study was terminated. Study 2 was stopped for business reasons before the planned interim analysis. NRS scores in week 8 were -1.98 (0.37), -1.60 (0.37), and -1.70 (0.38) for placebo (n = 26), desvenlafaxine 250 mg/d (n = 24), and pregabalin 450 mg/d (n = 21), respectively; neither active treatment differed significantly from placebo. Desvenlafaxine was generally safe and well tolerated. Efficacy of desvenlafaxine for pain associated with FMS was not demonstrated.
2. Ang DC, Jensen MP, Steiner JL, et al. Combining cognitive-behavioral therapy and milnacipran for fibromyalgia: a feasibility randomized-controlled trial. *The Clinical journal of pain*. 2013;29(9):747-754.
OBJECTIVES: To evaluate the feasibility of a randomized-controlled trial and to obtain estimates of the effects of combined cognitive-behavioral therapy (CBT) and milnacipran for the treatment of fibromyalgia., METHODS: Fifty-eight patients with fibromyalgia were randomized to 1 of the 3 treatment arms: (1) combination therapy (n = 20); (2) milnacipran+education (n = 19); and (3) placebo+CBT (n = 19). Patients received either milnacipran (100 mg/d) or placebo. Patients also received 8 sessions of phone-delivered CBT or educational instructions, but only from baseline to week 9. Assessments were conducted at baseline, week 9, and 21. The primary endpoints were baseline to week 21 changes in weekly average pain intensity and physical function (SF-36 physical function scale)., RESULTS: Compared with milnacipran, combination therapy demonstrated a moderate effect on improving SF-36 physical function (SE = 9.42 [5.48], P = 0.09, effect size = 0.60) and in reducing weekly average pain intensity (mean difference [SE] = -1.18 [0.62], P = 0.07, effect size = 0.67). Compared with milnacipran, CBT had a moderate to large effect in improving SF-36 physical function (mean difference [SE] = 11.0 [5.66], P = 0.06, effect size = 0.70). Despite the presence of concomitant centrally acting therapies, dropout rate was lower than anticipated (15% at week 21). Importantly, at least 6 out of the 8 phone-based therapy sessions were successfully completed by 89% of the patients; and adherence to the treatment protocols was > 95%. CONCLUSIONS: In this pilot study, a therapeutic approach that combines phone-based CBT and milnacipran was feasible and acceptable. Moreover, the preliminary data supports conducting a fully powered randomized-controlled trial.
3. Arnold LM, Sarzi-Puttini P, Arsenault P, et al. Efficacy and Safety of Pregabalin in Patients with Fibromyalgia and Comorbid Depression Taking Concurrent Antidepressant Medication: A Randomized, Placebo-controlled Study. *The Journal of rheumatology*. 2015;42(7):1237-1244.
OBJECTIVE: To assess pregabalin efficacy and safety in patients with fibromyalgia (FM) with comorbid depression taking concurrent antidepressant medication., METHODS: This randomized, placebo-controlled, double-blind, 2-period, 2-way crossover study was composed of two 6-week treatment periods separated by a 2-week taper/washout phase. Patients with FM (aged \geq 18 yrs) taking a stable dose of a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for depression were randomized 1:1 to receive pregabalin/placebo or placebo/pregabalin (optimized to 300 or 450 mg/day). Antidepressant medication was continued throughout the study. The primary efficacy outcome was the mean pain score on an 11-point numerical rating scale. Secondary efficacy outcomes included measures of anxiety, depression, patient function, and sleep., RESULTS: Of 197 patients randomized to treatment, 181 and 177 received \geq 1 dose of pregabalin and placebo, respectively. At baseline, 52.3% of patients were taking an SSRI and 47.7% an SNRI, and mean pain score was 6.7. Mean pain scores at endpoint were statistically significantly reduced with pregabalin (least squares mean difference from placebo -0.61, 95% CI -0.91 - -0.31, p = 0.0001). Pregabalin significantly improved Hospital Anxiety and Depression Scale-Anxiety (difference -0.95, p < 0.0001) and -Depression (difference -0.88, p = 0.0005) scores, Fibromyalgia Impact Questionnaire total score (difference -6.60, p < 0.0001), and sleep quality (difference 0.57, p < 0.0001), but not EuroQol 5-Dimensions score (difference 0.02, p = 0.3854). Pregabalin safety was consistent with previous studies and current product labeling., CONCLUSION: Compared with placebo, pregabalin statistically significantly improved FM pain and other symptoms in patients taking antidepressant medication for comorbid depression. ClinicalTrials.gov identifier: NCT01432236.

4. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis and rheumatism*. 2005;52(8):2495-2505.
OBJECTIVE: To assess the efficacy and safety of pramipexole, a dopamine 3 receptor agonist, in patients with fibromyalgia., METHODS: In this 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial, 60 patients with fibromyalgia were randomized 2:1 (pramipexole:placebo) to receive 4.5 mg of pramipexole or placebo orally every evening. The primary outcome was improvement in the pain score (10-cm visual analog scale [VAS]) at 14 weeks. Secondary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI). Patients with comorbidities and disability were not excluded. Stable dosages of concomitant medications, including analgesics, were allowed., RESULTS: Compared with the placebo group, patients receiving pramipexole experienced gradual and more significant improvement in measures of pain, fatigue, function, and global status. At 14 weeks, the VAS pain score decreased 36% in the pramipexole arm and 9% in the placebo arm (treatment difference -1.77 cm). Forty-two percent of patients receiving pramipexole and 14% of those receiving placebo achieved > or =50% decrease in pain. Secondary outcomes favoring pramipexole over placebo included the total FIQ score (treatment difference -9.57) and the percentages of improvement in function (22% versus 0%), fatigue (29% versus 7%), and global (38% versus 3%) scores on the MDHAQ. Compared with baseline, some outcomes showed a better trend for pramipexole treatment than for placebo, but failed to reach statistical significance, including improvement in the tender point score (51% versus 36%) and decreases in the MDHAQ psychiatric score (37% versus 28%), the BAI score (39% versus 27%), and the HAM-d score (29% versus 9%). No end points showed a better trend for the placebo arm. The most common adverse events associated with pramipexole were transient anxiety and weight loss. No patient withdrew from the study because of inefficacy or an adverse event related to pramipexole., CONCLUSION: In a subset of patients with fibromyalgia, approximately 50% of whom required narcotic analgesia and/or were disabled, treatment with pramipexole improved scores on assessments of pain, fatigue, function, and global status, and was safe and well-tolerated.
5. Luciano JV, Guallar JA, Aguado J, et al. Effectiveness of group acceptance and commitment therapy for fibromyalgia: a 6-month randomized controlled trial (EFFIGACT study). *Pain*. 2014;155(4):693-702.
In the last decade, there has been burgeoning interest in the effectiveness of third-generation psychological therapies for managing fibromyalgia (FM) symptoms. The present study examined the effectiveness of acceptance and commitment therapy (ACT) on functional status as well as the role of pain acceptance as a mediator of treatment outcomes in FM patients. A total of 156 patients with FM were enrolled at primary health care centers in Zaragoza, Spain. The patients were randomly assigned to a group-based form of ACT (GACT), recommended pharmacological treatment (RPT; pregabalin + duloxetine), or wait list (WL). The primary end point was functional status (measured with the Fibromyalgia Impact Questionnaire, FIQ). Secondary end points included pain catastrophizing, pain acceptance, pain, anxiety, depression, and health-related quality of life. The differences between groups were calculated by linear mixed-effects (intention-to-treat approach) and mediational models through path analyses. Overall, GACT was statistically superior to both RPT and WL immediately after treatment, and improvements were maintained at 6 months with medium effect sizes in most cases. Immediately after treatment, the number needed to treat for 20% improvement compared to RPT was 2 (95% confidence interval 1.2-2.0), for 50% improvement 46, and for achieving a status of no worse than mild impaired function (FIQ total score <39) also 46. Unexpectedly, 4 of the 5 tested path analyses did not show a mediation effect. Changes in pain acceptance only mediated the relationship between study condition and health-related quality of life. These findings are discussed in relation to previous psychological research on FM treatment.
6. Martin J, Torre F, Aguirre U, et al. Evaluation of the interdisciplinary PSYMEPHY treatment on patients with fibromyalgia: a randomized control trial. *Pain medicine (Malden, Mass)*. 2014;15(4):682-691.
OBJECTIVE: Fibromyalgia (FM) is a chronic disorder that can have a devastating effect on patients' lives. This study assessed the efficacy of a 6-week interdisciplinary treatment that combines coordinated PSYchological, Medical, Educational, and PHYsiotherapeutic interventions (PSYMEPHY) compared with standard pharmacologic care., DESIGN: The study was a randomized controlled trial (54 participants in the PSYMEPHY group and 56 in the control group [CG]) with follow-up at 6 months. PSYMEPHY patients were also assessed at 12 months. The main outcomes were changes in total Fibromyalgia Impact Questionnaire (FIQ) score, pain, fatigue, morning tiredness, anxiety, and use of pain coping strategies as measured by the FIQ, the visual analog scale, and the Coping with Chronic Pain Questionnaire. After the 6-month assessment, patients in the CG were offered the PSYMEPHY treatment, and completed all of the instruments immediately after treatment, and at 6- and 12-month follow-up visits (N=93)., SETTING: Subjects received therapy at two different outpatient clinical locations., PATIENTS: Fibromyalgia patients., RESULTS: Six months after the intervention, significant improvements in total FIQ score (P=0.04), and pain (P=0.03) were seen in the PSYMEPHY group compared with controls. Twelve months after the intervention, all patients in the PSYMEPHY group maintained statistically significant improvements in total FIQ score, and pain, and showed an improvement in

fatigue, rested, anxiety, and current pain compared with baseline. Data from the control patients who underwent the PSYMEPHY intervention corroborated the initial results, CONCLUSIONS: This study highlights the beneficial effects of an interdisciplinary treatment for FM patients in a hospital pain management unit. A 6-week interdisciplinary intervention showed significant improvement in key domains of fibromyalgia, as quality of life, pain, fatigue, rested, and anxiety at 12 months.

7. Mease PJ, Farmer MV, Palmer RH, et al. 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.
OBJECTIVE: To evaluate the safety, tolerability, and efficacy of adding milnacipran to pregabalin in patients with fibromyalgia who have experienced an incomplete response to pregabalin. METHODS: In this randomized, multicenter, open-label study, patients received pregabalin 300 or 450 mg/day during a 4- to 12-week run-in period. Patients with weekly recall visual analog scale (VAS) pain score of at least 40 and up to 90, Patient Global Impression of Severity score of at least 4, and Patient Global Impression of Change (PGIC) score of at least 3 were classified as incomplete responders and randomized to continue pregabalin alone (n = 180) or receive milnacipran 100 mg/day added to pregabalin (n = 184). The primary efficacy parameter was responder status based on PGIC score of up to 2. The secondary efficacy parameter was change from randomization in weekly recall VAS pain score. Safety parameters included adverse events (AEs), vital signs, and clinical laboratory tests. RESULTS: The percentage of PGIC responders was significantly higher with milnacipran added to pregabalin (46.4%) than with pregabalin alone (20.8%; $p < 0.001$). Mean improvement from randomization in weekly recall VAS pain scores was greater in patients receiving milnacipran added to pregabalin (-20.77) than in patients receiving pregabalin alone (-6.43; $p < 0.001$). During the run-in period, the most common treatment-emergent AEs with pregabalin were dizziness (22.8%), somnolence (17.3%), and fatigue (9.1%). During the randomized period, the most common treatment-emergent AEs with milnacipran added to pregabalin were nausea (12.5%), fatigue (10.3%), and constipation (9.8%). CONCLUSIONS: In this exploratory, open-label study, adding milnacipran to pregabalin improved global status, pain, and other symptoms in patients with fibromyalgia with an incomplete response to pregabalin treatment.
8. Moldofsky H, Harris HW, Archambault WT, et al. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. *The Journal of rheumatology.* 2011;38(12):2653-2663.
OBJECTIVE: To determine the effects of bedtime very low dose (VLD) cyclobenzaprine (CBP) on symptoms and sleep physiology of patients with fibromyalgia (FM), unrefreshing sleep, and the alpha-nonREM sleep electroencephalographic (EEG) anomaly at screening., METHODS: Of 37 patients with FM in the screened population, 36 were randomized and treated in this 8-week, double-blind, placebo-controlled, dose-escalating study of VLD CBP 1-4 mg at bedtime. We evaluated changes in subjective symptoms including pain, tenderness, fatigue, mood [Hospital Anxiety and Depression Scale (HAD)], and objective EEG sleep physiology (at screening, baseline, and Weeks 2, 4, and 8)., RESULTS: In the VLD CBP-treated group (n = 18) over 8 weeks, musculoskeletal pain and fatigue decreased, tenderness improved; total HAD score and the HAD depression subscore decreased; patient-rated and clinician-rated fatigue improved. In the placebo-treated group (n = 18), none of these outcome measures changed significantly. Compared to placebo at 8 weeks, VLD CBP significantly improved pain, tenderness, and the HAD Depression subscore. Analysis of cyclic alternating pattern (CAP) sleep EEG revealed that significantly more subjects in the VLD CBP group than the placebo group had increased nights of restorative sleep in which $CAP(A2+A3)/CAP(A1+A2+A3) = CAP(A2+A3(Norm)) \leq 33\%$. For VLD CBP-treated subjects, the increase in nights with $CAP(A2+A3(Norm)) \leq 33\%$ was correlated to improvements in fatigue, total HAD score, and HAD depression score., CONCLUSION: Bedtime VLD CBP treatment improved core FM symptoms. Nights with $CAP(A2+A3(Norm)) \leq 33\%$ may provide a biomarker for assessing treatment effects on nonrestorative sleep and associated fatigue and mood symptoms in persons with FM.
9. Oliván-Blázquez B, Herrera-Mercadal P, Puebla-Guedea M, et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain.* 2014;155(12):2517-2525.
Fibromyalgia (FM) is a prevalent and disabling chronic disease. Recent studies have found elevated levels of glutamate in several brain regions, leading to hypotheses about the usefulness of glutamate-blocking drugs such as memantine in the treatment of FM. The aim of this study was to evaluate the efficacy of memantine in the treatment of pain and other clinical variables (global function, clinical impression, depression, anxiety, quality of life) in FM patients. A double-blind, parallel randomised controlled trial was developed. A total of 63 patients diagnosed with FM were recruited from primary health care centres in Zaragoza, Spain. Memantine was administered at doses of 20mg/d after 1 month of titration. Assessments were carried out at baseline, posttreatment, and 3- and 6-month follow-up. Compared with a placebo group, memantine significantly decreased ratings on a pain visual analogue scale (Cohen's $d=1.43$ at 6 months) and pain measured with a sphygmomanometer ($d=1.05$). All other secondary outcomes except anxiety also improved, with moderate-to-large effect sizes at 6 months. Compared with placebo, the absolute risk reduction obtained with memantine was 16.13% (95% confidence interval=2.0% to 32.6%), and the number needed to treat was 6.2 (95% confidence interval=3 to 47).

Tolerance was good, with dizziness (8 patients) and headache (4 patients) being the most frequent side effects of memantine. Although additional studies with larger sample sizes and longer follow-up times are needed, this study provides preliminary evidence of the utility of memantine for the treatment of FM.

10. Ramzy EA. Comparative Efficacy of Newer Antidepressants in Combination with Pregabalin for Fibromyalgia Syndrome: A Controlled, Randomized Study. *Pain practice : the official journal of World Institute of Pain*. 2017;17(1):32-40.

BACKGROUND: This controlled, randomized study investigated the hypothesis that the combined use of pregabalin plus paroxetine for fibromyalgia management would be associated with comparable Somatic Symptoms Scale-8 (SSS-8) and Center for Epidemiological Studies Depression Scale (CESDS) scores, but higher tolerability than the combined use of pregabalin plus either amitriptyline or venlafaxine., **METHODS:** After institutional ethics committee approval, 75 female subjects diagnosed with fibromyalgia and in receipt of pregabalin (75 mg/day) were randomly allocated to concurrently receive amitriptyline (25 mg/day; n = 24), venlafaxine (75 mg/day; n = 25), or paroxetine (25 mg/day; n = 26). All patients were assessed bimonthly for 6 consecutive months for changes in SSS-8 and CESDS scores, life satisfaction, mood, sleep quality, fatigue, medication tolerability, and adverse events., **RESULTS:** Compared with pregabalin plus amitriptyline or venlafaxine, the combined use of pregabalin plus paroxetine in fibromyalgia patients resulted in significantly lower SSS-8 and CESDS scores from 18 (P < 0.05) and 10 weeks (P < 0.001) after the initiation of study medications, respectively; higher medication tolerability (P < 0.001); improved life satisfaction, mood, and sleep quality at most observation times (P < 0.05); and fewer instances of dry mouth and elevated blood pressure (P < 0.02). Medication termination due to poor tolerability was observed most frequently in the venlafaxine group (P < 0.05), while drowsiness, dizziness, blurred vision, abnormal taste, hunger, hallucination, urination problems, and sexual dysfunction were observed most frequently in the amitriptyline group (P < 0.02)., **CONCLUSION:** The combined use of pregabalin plus paroxetine offers an effective method with increased tolerability to reduce the somatic and depressive symptoms of fibromyalgia and to enhance the quality of life in affected individuals.

Appendix 4: Key Inclusion Criteria

Population	Patients with fibromyalgia
Intervention	Antidepressant, antiepileptic, or analgesic pharmacotherapy
Comparator	Placebo, other pharmacotherapy, or non-pharmacological therapy
Outcomes	Symptom improvement Functional improvement Quality of life Morbidity Mortality Severe adverse events Discontinuation due to adverse events
Setting	Outpatient

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for pregabalin?	Yes: Go to Renewal Criteria	No: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	Yes: Go to #4	No: Go to #5
4. Does the patient have a diagnosis of epilepsy?	Yes: Approve for lifetime	No: Go to #5

Approval Criteria		
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	Yes: Go to #6	No: Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	Yes: Approve for 90 days	No: Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	

Non-funded		
Fibromyalgia	X	

P&T Review: 7/18 (DM); 3/18; 3/17
Implementation: 8/15/18; 4/1/17

Milnacipran

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days

Requires PA:

- Milnacipran

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	Yes: Approve for 90 days	No: Go to #3. Pass to RPh.
3. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. The prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	
Diabetic Neuropathy	
Postherpetic Neuropathy	
Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	X

P&T Review: 7/18 (DM); 3/17

Implementation: 4/1/17