2022

Higher efficacy in the treatment of fibromyalgia with duloxetine and pregabalin combination than monotherapy

Joel Rose-Kamprath  
Wayne State School of Medicine, gm6860@wayne.edu

Follow this and additional works at: https://digitalcommons.wayne.edu/crp

Part of the Family Medicine Commons, Integrative Medicine Commons, and the Primary Care Commons

Recommended Citation

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.
Higher efficacy in the treatment of fibromyalgia with duloxetine and pregabalin combination than monotherapy

JOEL ROSE-KAMPRATH, Wayne State University School of Medicine, gm6860@wayne.edu

ABSTRACT
A clinical decision report using:


for a patient with chronic pain due to fibromyalgia.

Keywords: pregabalin, duloxetine, fibromyalgia, chronic pain

Clinical-Social Context

Ms. Julia Richardson (pseudonym), a 63-year-old Black woman (she/her) with past medical history of hypertension, chronic kidney disease (CKD), and anxiety presented to the emergency department with chronic back and lower extremity pain. Ms. Richardson also said, “I’m very tired all the time and I haven’t had a good night of sleep in months”. She had similar complaints six months prior that resolved spontaneously. Her symptoms have been attributed to fibromyalgia after extensive workup was negative for other sources of her pain. For the pain, Ms. Richardson has been taking twelve, 220 mg tablets of Naproxen with minimal relief. Ms. Richardson’s other medical problems are heart failure with preserved ejection fraction and paroxysmal atrial fibrillation. She smokes about half a pack of cigarettes per day for the past 25 years, a few beers on the weekends, daily marijuana use for the past 10 years, and denies any other illicit substance use. Ms. Richardson is single and lives alone at a homeless shelter where she has lived for the past year and a half. She has supplemental social security income, Medicaid health insurance, and she says that she feels safe and comfortable in her shelter. She has food security and has some family support in the area.

Ms. Richardson has been struggling with her pain for years with the addition of her lower extremity pain as a more recent complaint. She has taken non-steroidal anti-inflammatory medications and Tylenol with only slight relief of symptoms. She has also been prescribed gabapentin in the past again with only slight relief of her pain. Her living situation and comorbidities have limited her ability to add exercise or lifestyle changes to better manage her fibromyalgia. Due to inadequate pain relief with NSAID monotherapy and combination therapy of NSAIDs and gabapentin, alternative therapies were brought into discussion. It was also recommended that Ms. Richardson avoid NSAIDs because her CKD. She was started on pregabalin monotherapy which was able to provide her some pain relief, however she continued to complain of constant pain and difficulty sleeping. The team brought up the idea of adding duloxetine in combination with pregabalin due pain relief and drowsiness properties. She was willing to undergo any diagnostic procedures and medication recommendations to alleviate the constant pain.
Clinical Question

Is the combination therapy of duloxetine and pregabalin more effective than monotherapy for treating fibromyalgia?

Research Article


Description of Related Literature

A PubMed search with the key terms “pregabalin OR lyrica”, “duloxetine”, and “fibromyalgia” was conducted, yielding 151 results. All articles without the diagnosis of fibromyalgia or not involving the treatment with pregabalin or duloxetine were excluded. A “clinical trial” filter was used to narrow the results to only clinical trials which yielded 7 search results. However, there were some relevant studies not captured by this filter that will be discussed. Two additional relevant studies were found by using the “similar articles” feature from the article authored by Gilron et al. PMID: 26982602. Additionally, when the search was broadened to include other antidepressant combinations, another relevant study was found. Through these search criteria, the number of relevant studies was narrowed to 101-10.

In 2010, a study was published by Straube et al. that was a systematic review consisting of clinical trials focusing on the treatment of fibromyalgia with pregabalin. The study analyzed 5 clinical trials with a total of 3808 patients and the results showed significant pain reduction and sleep benefit in the groups taking pregabalin vs the placebo. This study was excluded because it was a systemic review, as opposed to a direct clinical trial, and it only focused on monotherapy with pregabalin.

A study conducted in 2014 by Lunn et al. was an update on the systematic review completed in 2010 to investigate the use of duloxetine for patients with neuropathic and nociceptive pain conditions. Patients with fibromyalgia who were given 60 mg of Duloxetine daily showed more than a 50% decrease in pain over 12 weeks when compared to patients that were given a placebo. Although this review included six studies with 2728 participants diagnosed with fibromyalgia, it was not used due to the lack of randomized-controlled trials (RCTs) showing efficacy of pregabalin and duloxetine combination therapy.

Kiso et al. completed a randomized-control study in 2018 to investigate the effects of pregabalin and duloxetine on neurotransmitters in the dorsal horn. This study used a rat model of fibromyalgia for the patient population. This study was not included because it focused on neurotransmitter levels and the use of a rat model lacks external validity for the human population with fibromyalgia.

Lee and Song published a study in 2016 that compared the efficacy of pregabalin, duloxetine, and milnacipran for treating fibromyalgia. This study was a meta-analysis that compared 9 RCTs in the Bayesian network that included 5140 patients. The RCTs showed that the proportion of patients that had over a 30% improvement in pain control from baseline was significantly higher in the experimental groups (pregabalin, duloxetine, or milnacipran) than the placebo groups. However, the authors concluded that there was no significant difference in efficacy and tolerability between the medications. This study showed that these medications were successful in RCTs to treat the pain of fibromyalgia, however the study was limited by the population chosen and that it did not include studies that tested combination therapies. This study was ultimately not included based on these reasons and that it was a meta-analysis.

A study by Staud et al. was published in 2008 that analyzed two different RCTs for duloxetine and pregabalin use in fibromyalgia. This study focused on how the design of the studies impacts placebo effects. This study was not included because it did not analyze the efficacy of pregabalin and duloxetine for fibromyalgia treatment.

A large study by Thorpe et al. was published in 2018. It was a systematic review that analyzed multiple different combination therapies and their effectiveness in treating fibromyalgia. The authors found that throughout the 16 studies analyzed, there was no convincing evidence to support or refute the use of combination therapy vs. monotherapy in fibromyalgia. This study was ultimately not used because it was a SR of multiple different RCTs that covered a variety of different combination therapies for fibromyalgia.
Bidari et al. published a RCT in 2019. This open-label trial compared the efficacy of pregabalin and duloxetine for the treatment of pain and depression in women diagnosed with fibromyalgia. This study was excluded because it only investigated the use of pregabalin and duloxetine monotherapies for the treatment of fibromyalgia.

A study published in 2014 by Irving et al. investigated a similar question and used similar medications during the trial. These authors investigated the safety and tolerability of duloxetine monotherapy vs. pregabalin monotherapy vs. duloxetine and gabapentin combination therapy. However, this study was ultimately excluded because the patient population that was investigated differed significantly from ours in that these patients were diagnosed with diabetic peripheral neuropathy as opposed to fibromyalgia.

Ramzy published a study of a RCT in 2017 that compared combinations of pregabalin and 3 different antidepressants in the treatment of fibromyalgia. The study concluded that the combination of paroxetine and pregabalin showed significantly reduced symptoms and increased quality of life compared to the other two combination therapies. This study was excluded because it only compared the efficacy of dual therapies and did not investigate differences between monotherapy and dual therapy.

The study ultimately selected was published in 2016 by Gilron et al. This is a randomized-control study comparing the efficacy of pregabalin and duloxetine combination therapy to monotherapy in patients with fibromyalgia. This study showed an improvement in multiple clinical outcomes in patients taking the combination therapy vs. placebo. It was selected because it was the only known clinical trial that analyzed the efficacy of combination therapy with pregabalin and duloxetine vs. monotherapy vs. placebo. This study agrees with the consensus of duloxetine and pregabalin as effective treatments for fibromyalgia and begins the process of analyzing the efficacy of combination therapies.

The Strength of Recommendation is A, based on multiple consistent randomized controlled trials.

**Critical Appraisal**

The study selected carries Level 2 evidence according to the Oxford Center for Evidence Based-Medicine and a B-level recommendation according to the Strength of Recommendation Taxonomy. Patients were recruited over a 3-year period with 47 ultimately being screened and 41 patients chosen to participate in the study. Patients that had another primary pain condition other than fibromyalgia were excluded as well as patients with uncontrolled comorbid conditions.

41 patients participated in the clinical trial with age ranges from 20 to 71 years old with the mean age at 56. The recruitment was hindered by difficulty for trial candidates to discontinue pretrial antidepressants. The small size of this study may have affected the reliability due to increased variance and potential bias. This study may not have significant external validity. Most of the patients were female (88%) and Caucasian (98%). Both the mean age and gender identity of the study population are similar to our patient who is a 63-year-old female. The study was unclear about the methods in which patients were recruited, which may have led to some participation bias. Thus, the study population may be systematically different than the target population. This could also limit the external validity of this study. The study was a single-center, 4-period (with 6 weeks per period) crossover randomized double blinded trial. Participants were randomly placed in 1 of 24 sequences for the 4 periods. Medications and placebo were given in identical capsules. 39 patients were able to complete at least 2 periods of the study before stopping due to adverse effects. Controls groups were individually based during the period in which participants only received a placebo pill. The crossover design allowed for treatment comparison within each patient.

To keep patients comfortable during the placebo phase and washout phase, patients were allowed to use previously prescribed analgesics such as acetaminophen, NSAIDs, and opioids (<200 mg equivalents/day) at a steady dose. All procedural therapies were forbidden (i.e. nerve block). This may have had some impact on the reports of pain and the perceived efficacy of the trial medications.

Participants of the trial completed a baseline pain diary for 7 days which was used as a comparison tool to get an accurate measure of change in pain during each of the trial periods. Each trial period was 6 weeks long with the first 24 days dedicated to escalating the dose of the trial medication to the maximum tolerated dose (MTD) based on adverse effects. The primary outcome analyzed was average pain intensity over the past 24 hours. This was obtained in the morning and rated on a scale from 0-10, then averaged over 7 days at the MTD. The authors’ rationale for using this as the primary outcome was that pain sensitivity is the most sensitive to
treatment. This primary outcome is clinically relevant because pain is the primary complaint of patients with fibromyalgia. The secondary outcomes were “worse pain intensity in the past 24 hours”, “average nocturnal pain intensity”, “global pain relief”, and a host of other measures.

Results were analyzed based on the period with the medication given compared to the placebo period and baseline pain for each individual participant. Pain with combination was lower than placebo (p<0.001) and pregabalin (p<0.001). Pain with duloxetine alone was lower than placebo (p<0.001) and pregabalin (p<0.003). However, the comparison of combination therapy to duloxetine alone was not significantly different with a P-value of 0.09. For secondary outcomes, there was a significant increase in moderate global pain relief between combination and duloxetine (p=0.03), combination and pregabalin (p=0.02), combination and placebo (p<0.0001), and duloxetine and placebo (p=0.04). These results preliminarily show that a combination therapy of duloxetine and pregabalin may be more efficacious than pregabalin alone, but not duloxetine alone. More extensive studies with larger, more diverse populations need to be tested to gather more accurate data that can be extrapolated to the general population.

**Clinical Application**

Ms. Richardson has been suffering with the pain of her fibromyalgia for quite some time. She has tried to manage it on her own and with over-the-counter medication, but it has come to the point at which she is unable handle the pain and lack of sleep. She had been unable to add exercise and lifestyle changes to help manage the pain due to her living situation and comorbidities. The team began her on pregabalin therapy because Ms. Richardson stated that gabapentin had not helped in the past. Ms. Richardson lives in a homeless shelter and has lived there for a few years. She told us that this pain and her living situation has made it difficult for her to regularly see her primary care. Her finances and transportation are major barriers for her in receiving the necessary healthcare to control her chronic pain. Thus, it was imperative to our team to find a medication regimen that adequately treated her pain before we discharged her back to her shelter.

After the pregabalin monotherapy was unable to relieve Ms. Richardson’s pain nor her sleep, we discussed with her the potential of adding on duloxetine in combination with pregabalin. We explained that duloxetine has the side effect of drowsiness that may be beneficial for her. She was receptive to the idea of adding on this medication in desperation for pain relief and sleep. Ms. Richardson asked about the risks of adding on this new medication. We discussed with her that the potential risks of combination therapy compared to monotherapy are very minimal with the only significant factor being increased drowsiness. We as a team believed that this small risk was outweighed by the potential benefit of adding on duloxetine therapy and Ms. Richardson agreed with our proposal.

It was communicated to Ms. Richardson that there has been research done that shows a potential benefit of combination therapy, but there is not an overwhelming amount of evidence yet. The conclusion of this one study was that combination therapy was more effective for pain control and secondary symptomatic control than pregabalin. She decided that the potential benefit of the combination therapy was enough for her to try the new regimen. With this new regimen, Ms. Richardson was able to have more adequate pain relief and sleep improvement. Her success agrees with the results of the study.

The study itself shows internal validity in that there are significant changes in primary and secondary outcomes with the administration of different medication regimens. The results clearly show that a combination therapy is more efficacious than pregabalin monotherapy or placebo. However, there is no evidence showing a significant difference between combination and duloxetine monotherapy. Based on the limitations of the study, population size and demographics, this study has only some external validity.

**New Knowledge Related to Clinical Decision Science**

By talking with Ms. Richardson and getting an extensive history about her and the pain she has been feeling, our team was able to guide clinical decision making and decide on the best next steps for our patient. Fibromyalgia is a diagnosis of exclusion and thus a detailed history of her pain, past treatments, imaging, and lab work are key to ruling out other potential causes of her chronic pain.
By knowing that she has been unable to fully manage her pain with long term NSAIDs, gabapentin, and pregabalin monotherapy, has had difficulty sleeping, and has significant barriers to lifestyles changes, our team felt like she was an ideal candidate for combination therapy of pregabalin and duloxetine. Also, the difficulty of her living situation, lack of transportation, and lack of access to healthcare made it a priority for our team to find a successful medication regimen while she was under our care. Although Ms. Richardson had been compliant with medication regimens in the past, she had been unable to follow up to assess treatment failures. The importance of following up with her primary care physician (PCP) was emphasized with her. Our team made it a priority to provide Ms. Richardson with a PCP that was located close to her shelter, and we provided her with transportation resources to make sure she successfully followed up after discharge.

Conflict Of Interest Statement
The author declares no conflicts of interest.

References