Safe & Effective?

Reported by Tamara K. Liller, M.A.

Three drugs are currently licensed by the FDA for fibromyalgia. They have been on the market for a significant length of time, but many clinicians and patients are still unsure just how they "stack up" against each other and other FM drugs. Independent assessments are greatly needed. While we wait, preliminary reports from three prominent experts deserve attention. Highlights are offered below.

"Comparative Efficacy And Harms Of Duloxetine, Milnacipran, And Pregabalin In Fibromyalgia Syndrome"

In Germany, researchers Winfried Häuser, Frank Petzke, and Claudia Sommer recently joined forces to conduct a systematic review of the research trials that have been conducted on fibromyalgia (FM) patients for the two serotonin and norepinephrine reuptake inhibitors (SNRI's) duloxetine (Cymbalta) and milnacipran (Savella) , and the antiepileptic drug, pregabalin (Lyrica). Their resulting article appeared in the June 2010 issue of *The Journal of Pain*, published by the American Pain Society.[1] What the researchers wanted to know was:[2]

"Are the patients of the randomized controlled trials with duloxetine, milnacipran, and pregabalin comparable to those in clinical practice?

Are there differences in the efficacy between the three drugs to reduce FM symptoms?

Are there differences regarding the side effects and contraindications of the three drugs?"

To answer these questions, they conducted an exhaustive search of published research studies on the three drugs using the giant databases of Medline, Scopus, and Cochrane Central Register of Controlled Trials to locate randomized, controlled trials. They also scoured the websites of the Food and Drug Administration, the National Institutes of Health, and PhRMA (Pharmaceutical Research and Manufacturers of America) looking for unpublished data. They contacted the medical information departments of drug company sponsors and the first authors of studies already in print, among other sources, to find missing or additional data. In the end, 17 studies with 7,739 patients fit the inclusion criteria for quality which the researchers had prespecified.

It turned out that no "head-to-head" comparison studies of the three FM drugs had been performed. In addition, all of the available published studies had been initiated by pharmaceutical companies which raised questions of possible bias in favor of the products in the study results.[2]

The researchers found that patients with fibromyalgia had been recruited for participation in the drug trials from all over the world, though most were from the United States. However, no patients under the age of 18 nor over the age of 70 had been included. Also excluded were those with "unstable somatic diseases" (including inflammatory rheumatic disorders) as well as those with severe mental disorders, except in the duloxetine studies which included subjects with major depression. The length of the trials was relatively short-term, which the researchers found odd for a medical condition such as fibromyalgia which is usually considered a lifelong disorder. In addition, other conditions which existed simultaneously with FM (along with the medications taken for them) often went unreported. Finally, all of the drug trials permitted co-therapies along with the experimental drugs being studied. In the duloxetine and pregabalin trials, those allowed were aspirin and acetaminophen. In the milnacipran trials, they were hydrocodone and stable doses of NSAIDs, aspirin, and acetaminophen.[3]

Further analysis demonstrated that there were significant differences among the three drugs in average symptom reduction:[4]

- Duloxetine and pregabalin were superior to milnacipran in addressing pain and sleep disturbances.
- Duloxetine was superior to milnacipran and pregabalin in improving depressed mood.
- Milnacipran and pregabalin did a better job than duloxetine in reducing fatigue.
- Pregabalin had a lower risk of nausea or headache than duloxetine and milnacipran.
- The risk of diarrhea was higher for duloxetine than with the other two drugs.

In their journal article, Häuser et al., also indicated that one of the main methodological problems they faced in their review was the absence of standardized methods to rank subjective adverse events (for example, nausea). They also noted that some trials did not report harmful events reliably.

One particularly valuable set of findings which the investigators included in their article was a list of caveats for potential users of the three drugs which included the following:[5]

1. **Patients with unstable hypertension or chronic liver disease** should use duloxetine or milnacipran with caution.
2. **When depression is co-morbid with fibromyalgia,** individuals taking milnacipran or duloxetine should be monitored for suicidal thoughts or signs of aggression.
3. **When gastrointestinal issues like dyspepsia or irritable bowel syndrome are present in a patient,** pregabalin might be the best drug choice.
4. **FM patients who also have tension or migraine headaches** need to keep an eye on the severity of headaches when either duloxetine or milnacipran is taken.
5. **FM patients with chronic heart failure or obesity** should use pregabalin with caution. In addition, the neurocognitive side effects of pregabalin such as confusion, disturbed attention, and euphoric mood might dictate limited use in patients with severe "fibro fog."

Häuser, Petzke, and Sommer amassed a lot of invaluable information in their critical review, and their article is worthy of attention, particularly in suggesting which patients may be harmed by the new drugs. The fact remains that independent, "head-to-head" studies comparing the three FDA-approved drugs are still crucial.

References

1. Häuser W, Petzke F, Sommer C. "Comparative Efficacy and Harms of Duloxetine, Milnacipran, and Pregabalin in Fibromyalgia Syndrome." *The Journal of Pain*. June 2010; 11(6):505-521.
2. Ibid, p. 506.
3. Ibid, p. 507.
4. Ibid, p. 505.
5. Ibid, p. 518.

"Pharmacological Treatment Of FMS: New Developments"

University of Florida-Gainesville researcher Roland Staud, M.D., offers an extremely useful comparative analysis of medications for fibromyalgia in a lead article recently published in the journal, *Drugs*.[1] His analysis covers not only the three FDA-licensed drugs, duloxetine, milnacipran, and pregabalin but also the older "standby" medications which have been on the market for a much longer period and have undergone more thorough study. Staud considers the mechanism of action for each drug (if known) and its effectiveness based on available research; he includes adverse side effects where relevant. He also discusses some non-pharmacologic treatments

Like Hauser et al., in the article reported above, Staud is concerned about the unavailability of direct comparisons of drugs. He notes: "Although future therapies with any combination of these interventions will probably be beneficial for patients with fibromyalgia, only head-to-head comparison trials will provide evidence for the superiority of one treatment over another."[2]

Dr. Staud's first remarks about pharmaceutical agents concern drugs that existed well before the FDA approval of duloxetine, milnacipran, and pregabalin, and they are quite positive. He states: "Some of the most effective pharmacological therapies for fibromyalgia pain include low doses of tryicyclic antidepressants." He adds: "TCAs, particularly amitriptyline and the chemically similar muscle relaxant cyclobenzaprine, can improve the symptoms of pain, poor sleep, and fatigue associated with fibromyalgia."[3]

Staud also offers supportive evidence for the effectiveness of the drug, tizanidine, in lowering cerebrospinal fluid neuroamines and substance P in FM patients and for the analgesic drug, tramadol (in combination with paracetamol/acetaminophen),

in relieving pain. Also promising, but still being studied for possible use in the treatment of FM are several other medications. These include the NMDA receptor antagonists, ketamine and dextromethorphan; the cannabinoid nabilone; the anti-fatigue stimulant, modafinil; and the microglia-inhibitor, naltrexone. Staud appears upbeat about the prospects of sodium oxybate for the treatment of insomnia but is disappointed in the results of randomized, controlled trials for dopamine receptor antagonists compared to earlier, more promising, pilot trials.[4]

Dr. Staud describes the newer FDA-licensed drugs (duloxetine, milnacipran, and pregabalin) overall as follows: "In general, about half of all treated patients seem to experience a 30% reduction of symptoms, suggesting that many patients with fibromyalgia will require additional therapies."[5]

Duloxetine, which is a SNRI now FDA-approved for the treatment of pain associated with diabetic neuropathy and fibromyalgia and for major depressive disorder, appears to have different effects on men compared to women. Staud notes that in a randomized, controlled trial of 207 FM patients, men with FM did not experience a significantly greater response to duloxetine than to placebo.[6] The most common side effects of duloxetine appear to be nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, and dizziness.[7]

Milnacipran, also considered an antidepressant, is sometimes referred to as a NSRI (vs. a SNRI) because it puts more emphasis on the reuptake inhibition of norepinephrine over serotonin. When taken twice daily in a Phase II, randomized, controlled trial, milnacipran was superior to placebo, and side effects (nausea and headache) were reported as mild.[8] No mention is made of suicidal thoughts or concerns about hypertension or liver function in patients taking milnacipran (or duloxetine) as Hauser et al., point out in their article.

Similar to gabapentin (Neurontin), another anti-epileptic drug used to treat neuropathic pain which was studied not long ago via a NIH-funded grant, is pregabalin for which there is "strong evidence for a moderate reduction of fibromyalgia pain" as well as improved sleep, health-related quality of life, and small improvements in fatigue.[9] Reported adverse effects in the clinical trials prior to FDA acceptance included dizziness (which increased with higher dosages), sleepiness, dry mouth, edema in the periphery of the body, and weight gain.[10]

One of the most interesting aspects of the review offered by Dr. Staud is a formula he presents at the end for the pharmacological treatment of FM. It consists of four parts:[11]

1. Reduction of pain in the periphery of the body, muscular pain especially;
2. Improvement or prevention of central sensitization;
3. Normalization of sleep abnormalities; and
4. Treatment of negative affect (i.e., depression).

He further describes a specific strategy as follows.

"The first strategy is most likely to be relevant for acute fibromyalgia pain exacerbations and includes physical therapy, muscle relaxants, muscule injections, and analgesics. Central sensitization can be successfully ameliorated by cognitive behavioural therapy, sleep improvement, antidepressants, NMDA receptor antagonists, and anti-epileptics. Sleep dysfunction can be normalized by stress reduction, aerobic exercise, and GABA agonists. The pharmacological and behavioural treatment of secondary pain affect (anxiety, anger, depression, and fear) is equally important and may currently be one of the most powerful interventions for fibromyalgia pain."[12]

References

1. Staud R. "Pharmacological Treatment of Fibromyalgia Syndrome: New Developments." *Drugs* 2010; 70(1):1-14.
2. Ibid, p.11.
3. Ibid, p. 3.
4. Ibid, pp. 4-10.
5. Ibid, p. 1.
6. Ibid, p. 6.
7. Ibid, p. 7.
8. Ibid, p. 7.
9. Ibid, p. 6.
10. Ibid, p. 6.
11. Ibid, p. 10.
12. Ibid, p. 10-11.

The European Perspective

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) is the European Union's counterpart to the U.S. Food and Drug Administration. However, the CHMP's reaction has been quite different from the FDA's in terms of their willingness to approve duloxetine, milnacipran, and pregabalin for the treatment of fibromyalgia. In fact, the agency has not licensed any of the drugs for FM, even though all

three medications have been approved in Europe for other medical conditions.[1] Duloxetine was approved in 2004 for the treatment of the peripheral neuropathy of diabetes, urinary stress incontinence, and anxiety/depression. Milnacipran has been sold as an antidepressant in Europe since 1997 and in Japan since 2000. Pregabalin was authorized in 2004 for the treatment of neuropathic pain and epilepsy and later in 2006 for generalized anxiety. So what was the problem with fibromyalgia?

In the case of all three drugs, the CHMP was not reportedly impressed with their level of effectiveness in the treatment of FM in either the short or long term which was described as quite modest or minimal. In addition, the benefits of the drugs were not perceived as outweighing their risks.[2]

A different type of comment was offered by the European Network of Fibromyalgia Associations in response to the denial of duloxetine. In an official statement, the Association stated: "*It is suspected that the misperception, even among some medical professionals, in Europe that [fibromyalgia] is not a real medical condition must have contributed to the decision*."[3]

From the European medical research community came a more critical analysis of the research performed specifically on the drug pregabalin which was published in a journal article in *Tidsskr Nor Laegeforen* in June 2010 by the Norwegian researcher, Holtedahl, who reviewed available research on pregabalin in Medline and public trial registries.[4] The resulting analysis contained comments reminiscent of Hauser et al.: that all of the drug trials for pregabalin had been sponsored by one pharmaceutical company; negative drug results were seldom mentioned in the abstracts; and secondary endpoints were reported incompletely.[4] The article concluded that: "Recommendations for pregabalin in treatment of patients with fibromyalgia are based on rather weak evidence. Until trials independent of industry-funding are published, the role of pregabalin in the treatment of fibromyalgia remains unclear."[5]

References

1. See "European CHMP Adopts Negative Opinion on Cymbalta for the Treatment of Fibromyalgia," www.pharmanews.eu, 10/27/08. Also, "Questions and Answers on Recommendations for the Refusal of a Change to the Marketing Authorizations for Lyrica," European Medicines Agency (EMEA), London, April 2009. Also, "CHMP Rejects Drugs from Pierre Fabre and Pfizer in Fibromyalgia." APM Health Europe, http://health.apmnews.com 7/24/09. Also, "Milnacipran (Savella) Fails To Alleviate Fibromyalgia Pain, Has Safety Concerns," *Worst Pills, Best Pills News*, Public Citizen, September 2009;15(9).
2. Ibid.
3. "European Medicines Agency Rejects Cymbalta Approval," Press release 10/27/08, www.linzworld.wordpress.com.
4. "Pregabalin For Fibromyalgia - Can We Rely On The Pharmaceutical Industry" *Tidsskr Nor Laegeforen*, May 20, 2010; 130(10):1032.
5. Ibid.