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Summary of pharmacological therapies approved for FM

Fibromyalgia (FM) has received a lot more attention over the last couple of years through television and magazine advertisements promoting three new drugs indicated for use in FM. Lyrica (pregabalin), Cymbalta (duloxetine), and Savella (milnacipran) were approved by the Food Drug Administration (FDA) as effective treatments for FM based on their performance in clinical trials. In order to meet the FDA criteria as "effective" treatments, these drugs had to show benefits or some measurable level of improvement in study participants as they compared to placebos (substances with no active ingredients) in each their own trials. These medications might provide considerable relief for some patients, but they do not work the same way for everyone with FM, for a number of reasons.

These particular drugs differ from each other in their chemical composition and modes of action (i.e., they target different brain chemicals). Therefore, how each patient responds to any one of these will greatly depend on his or her own body chemistry, variation in symptoms, and severity of illness. The majority of FM patients have pain and disrupted sleep, but some may find mood disturbances to be problematic, while others have digestive, intestinal or bowel sensitivities. It is not unusual for FM patients to be prescribed multiple medications, to manage multiple symptoms, which may put some patients at a greater risk of adverse drug interactions.

Whenever new treatments are being contemplated, the general rule is to select a drug where its benefits are thought to outweigh the potential risks, and anything else known about the patient's medical history that might negatively impact him or her. In addition, when starting out any new medication, it is usually recommended that individuals with FM begin with a very low dose (i.e. 25% of prescribed dose) and work their way up slowly to the full prescribed dose, watching for any adverse side effects. This particularly applies to these drugs.

Despite their limited "track records" there often tends to be an eagerness to try out the latest treatments. Decisions to initiate treatment are often based on favorable study results (i.e., the acceptance of study results at face value) and may not take into account other factors that

influenced results (i.e., the severity of illness in the study participants or the placebo effect that produced favorable response). The result is the possibility of unrealistic expectations for the typical FM patient, who may have a more complicated history or combination of problems than study participants.

A group of German doctors conducted an extensive review of these three drugs on their overall efficacy, benefits and adverse effects, with one significant difference—they evaluated how they measured up to each other. Their comparative analysis was published in the Journal of Pain, the official scientific journal of the American Pain Society. Their findings and excerpts from several other studies are examined later in this article. But first, we will review the basic properties of these medications and the developments since their release on the market.

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Basics about medications approved for use in FM

Pregabalin (Lyrica) - The FDA approved Lyrica, made by Pfizer, Inc., in June 2007 as the first prescription medication for the treatment of FM. Very simply, Lyrica is thought to work by changing the effect of GABA (gamma amino butyric acid), often referred to as a "calming" neurotransmitter/brain chemical. Structurally, it is related to Pfizer's first antiepileptic drug, gabapentin (Neurontin), which came on the market in 1983. Lyrica is found to be more potent and effective at lower doses than gabapentin (Neurontin). Its primary uses in FM are for pain relief and improvement of fatigue and sleep.

An "informal" review of several internet drug information sources show that patients' experiences with Lyrica varied widely, from stating that it caused many difficult side effects, rapid weight gain, and the drug was found to be very expensive, to praising it as the best treatment they've used to date. The average of the patient/user ratings placed Lyrica at slightly beyond the halfway point on the scale used. This information is meant to provide a general idea in how a random group of patients responded to this treatment—it is strictly subjective and not a medical interpretation. Lyrica is also used to treat diabetic nerve pain, nerve pain after shingles and partial onset seizures in adults with epilepsy.

The most common side effects are weight gain, swelling of hands and feet, and may worsen "fibro fog" in some patients. In some clinical trials, dizziness and somnolence were the most frequently reported adverse events. Many of these side effects were echoed in the

above-mentioned patient/user reviews. It is important to report any unusual reactions to the prescribing physician, as some of these could be serious and warrant discontinuation of treatment—such as loss of coordination, uncontrolled movements, unusual fatigue, difficulty speaking or changes with vision. Some patients have experienced depression, changes in their mood or have had suicidal thoughts. As a result, effective April 2009, Lyrica and Neurontin (along with other antiepileptic drugs) are required by the FDA to include a warning about the increased risk of suicidal thoughts or actions on their product labels.

Duloxetine (Cymbalta) - In June 2008, Cymbalta, manufactured by the Lilly Co., was approved by the FDA for use in FM, to help reduce pain and improve function. Cymbalta belongs to a class of medications called selective SNRIs (serotonin and norepinephrine reuptake inhibitors). It works by increasing the activity of these two neurotransmitters which are found to be deficient in FM. By adjusting in how the brain and spinal cord respond to painful stimuli (which is part of the nociception system/how pain is sensed), is how it is thought to provide an analgesic effect. Cymbalta is also indicated for the treatment of major depressive disorder, generalized anxiety disorder, management of diabetic peripheral neuropathic pain, and more recently, it was approved for the management of chronic musculoskeletal pain, including chronic osteoarthritis pain and chronic low back pain.

Though Cymbalta is suggested for a wide range of problems, it still should be approached as a potent treatment with a dual mechanism. A thorough assessment should be made of the patient's personal and/or family history of psychiatric problems (e.g. bipolar/manic-depressive disorders) as this drug may worsen or uncover these.

It is also very important to review all medications used by the patients (including over-the-counter products and supplements) in order to prevent serious interactions since one-fourth of all prescribed medications are metabolized by the same enzyme (CYP2D6). These medications include other selective serotonin reuptake inhibitors (SSRI's), tricylic antidepressants (TCA's), beta-blockers, opiates, antiarrhythmics, migraine headache treatments, and various plant substances. For their own safety, patients need to communicate with their doctors in an honest, open manner, and not withhold any information about what else they might be using on their own (including alcohol), and use medications exactly as prescribed. In the event of adverse effects, patients need to inform their doctors about these problems and not make changes on their own.

NCBI warning for medication-induced suicidal tendencies. The National Center for Biotechnology Information (NCBI, a branch of the National Institutes of Health (NIH)) has posted an important ***warning about***

the potential risk of suicidal tendencies in some patients while using certain antidepressants, including but not limited to duloxetine (Cymbalta).

The NCBI advises that "all" patients should be informed about this risk and the early signs/symptoms associated with this risk. Family members or caregivers should know the same, so they can recognize warning signs. The reason for extra precautions, according to NCBI, is because people's mental health can change unexpectedly, even in individuals who do not have mental illness, but are using duloxetine to treat other conditions. This appears to happen, more often, at the beginning of treatment and/or when the dose is increased or decreased; therefore, their recommendation is that patients be closely monitored during these times. NCBI lists the following symptoms as potential warning signs of suicidal tendencies which need to be immediately reported to the doctor: "new or worsening depression; thinking about harming or killing yourself, or planning or trying to do so; extreme worry; agitation; panic attacks; difficulty falling asleep or staying asleep; aggressive or hostile behavior; irritability; acting without thinking; severe restlessness; frenzied abnormal excitement; or any other unusual changes in behavior."

Milnacipran (Savella) - Savella was approved by the FDA in January 2009 as yet another FM-appropriate treatment. It is made by Forest Laboratories Inc., and falls into the same class of medications as Cymbalta. However, its mechanism focuses on boosting norepinephrine levels more so than serotonin ones. Its overall ability to reduce pain has been reported by several sources as being only "marginal." Two of its more frequent side effects are increase in blood pressure and nausea. According to the NCBI, milnacipran is currently not used in the U.S. to treat depression. The NCBI has issued the same warnings for milnacipran as for duloxetine regarding potential changes in mood and/or risk of suicidal thoughts and tendencies.

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How do these medications compare to each other

A group of German doctors retrieved and reviewed data from previous studies conducted for all three pharmacological therapies, totaling 17 studies and 7,739 patients who met the inclusion criteria. (Such a study is called a meta-analysis.) Some of their sources included MEDLINE, SCOPUS, Cochrane Central Register of Controlled Trials, as well as unpublished data from FDA and NIH databases and others. Even though these studies may have some variations in how they were conducted, the amount of data reviewed was quite substantial. (*See our editorial note at the end of this article concerning the validity of such meta-analyses such as this one.*

) The article is written by Hauser W, et al, titled "Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome", and was published in the Journal of Pain, 11: 505-521, 2010.

One of the most remarkable findings in their analysis of these medications and their ability to reduce pain was that "adjusted indirect comparisons indicated no significant differences for 30% pain relief." This suggests that none of these were found to be highly effective against pain and they all seemed to be about the same, when evaluating degree of pain relief. When combining pain and sleep disturbances, duloxetine (Cymbalta) and pregabalin (Lyrica) were found to be considerably more effective than milnacipran (Savella). Milnacipran (Savella) and pregabalin (Lyrica) were more beneficial in reducing fatigue than duloxetine (Cymbalta), while duloxetine had a stronger impact on mood. Both SNRI's caused more headaches and nausea/digestive symptoms and also raised blood pressure. This comparison of specific features of these medications may be very helpful in a clinical setting as physicians try to select the most suitable treatment for each individual patient.

Though the level of pain relief or other noted improvements can be modest, or even minimal in some cases, drugs can still meet approval by the FDA. As mentioned above, pharmaceutical companies only need to show that a drug performs better than a placebo. For example, *Medical News Today*
reports the following data on clinical trials testing Cymbalta's effectiveness for FM: "Lilly established the efficacy of Cymbalta in two pivotal three-month clinical trials involving 874 patients with fibromyalgia. In both studies, Cymbalta reduced pain at study endpoint compared with placebo as measured by the Brief Pain Inventory (BPI) ... improvement in pain for Cymbalta vs. placebo was observed in the first week of each study. Fifty-one percent and 55 percent of patients on Cymbalta had a 30 percent improvement on the BPI at endpoint (clinically meaningful relief is considered at least 30 percent pain reduction)."

Some physicians are not convinced that all new drugs are better just because they are new, generally speaking, since this applies to treatments indicated for other conditions. The reason for their doubts is that the effectiveness/benefits of new drugs are not often compared to existing drugs. In one unusual case, clinical trials for a new drug that was supposed to be promoted as another treatment for FM were abruptly terminated by Pfizer in February 2009. The *"Musculoskeletal Report"* (a source for Biopharm business news) announced that Pfizer had re-evaluated this drug, esreboxetine, and concluded its potential benefits to FM patients would not be too substantial. The President and General Manager of Pfizer's Primary Care Business Unit, Pedro Lichtinger issued this statement, "While confident in the safety of these compounds, we don't believe that they provide significant benefit over other therapies." Esreboxetine was a selective norepinephrine reuptake inhibitor that Pfizer, Inc. was working on for use in FM. It is thought to be essentially the same drug as reboxetine (Edronax), also made by Pfizer, but

currently approved as a treatment for depression. Though one can only speculate about the potential value this drug might have had for FM (or not), it becomes all the more evident that "head to head" trials (i.e., studies in which one drug is directly compared to another drug or drugs from the same class or group) might be the best way to demonstrate the advantage of one treatment over another.

Recommended Reading:

"Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome" - Journal of Pain, Volume 11, Issue 6, June 2010, Pages 505-521, Authors: Winfried Häuser, Frank Petzke and Claudia Sommer. Full text article can be accessed at the Journal of Pain website.

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Editorial Comment on Statistical Meta-analysis

The Massachusetts CFIDS/ME and FM Association would like to bring to the attention of our readers that the type of study conducted by the group of German doctors discussed in this article is referred to as a "meta-analysis." This term refers to the statistical analysis of a group of individual studies. The authors of a meta-analysis re-analyze the results of many smaller studies (with only the limited information available in each published report of a study, not the original data from each) pooled as if a larger study had been done with all of the patients in the smaller studies. Thus a meta-analysis will take results from 10 studies of 10 patients each and claim to have valid results from 100 patients, but without having access to the original data for each of the 100 patients.

Thus a meta-analysis, in itself, is not an actual scientific study, but a type of averaging of averages from many different studies. Therefore, from a mathematical and also a medical standpoint, trying to get "effectiveness" data comparing drugs from varying studies that only compared a single drug to placebo is not really valid. There are too many factors that can throw one's conclusions off such as variations in study length, severity of FM in patients of different studies, numbers of dropouts in a study due to severity of side-effects, etc. So the German meta-analysis is similar to comparing apples to oranges (placebo), persimmons to oranges and redwood trees to oranges, and then coming up with conclusions about how apples, persimmons and redwood trees compare to each other. On the other hand, the German meta-analysis provides a broad review of a large number of studies. It is worth considering its conclusions, but they really shouldn't be taken as "gospel."

To put things even more into perspective, some time ago a meta-analysis of treatments for CFS found that Cognitive Behavioral Therapy (CBT) was the "best" treatment for CFS. The fact that most of the studies analyzed used the Oxford definition of CFS and compared CBT to placebo, and only a few of the analyzed studies looked at other treatments and patients identified by the 1988 or 1994 definitions of CFS, was ignored. Thus, the conclusion of a meta-analysis can be heavily influenced by the number of studies of a certain treatment outweighing the number of studies looked at in the analysis that used a different treatment. We don't know if that is the case in this German study, but it could be.

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