

Milnacipran for Fibromyalgia

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Summary

- ✓ **Milnacipran is an antidepressant that is under investigation for the treatment of fibromyalgia (a chronic pain disorder).**
- ✓ **Preliminary evidence suggests that milnacipran may benefit some patients with fibromyalgia, but adverse effects may limit its use.**
- ✓ **Complete results of phase 3 trials have not yet been published. Further studies are needed to evaluate the safety and efficacy of milnacipran, determine optimal dosing, confirm if beneficial effects are sustained, and clarify the drug's role relative to, and in conjunction with, other treatments for fibromyalgia.**

Background

About 2% to 3% of adult Canadians suffers from fibromyalgia, a chronic musculoskeletal pain disorder.^{1,2} Fibromyalgia most commonly begins to affect women between 20 to 50 years of age.¹ It causes significant work-related disability in 10% to 30% of those affected³ and negatively affects quality of life to a similar degree as rheumatoid arthritis.⁴ Diagnosis of fibromyalgia is complex and treatment options are limited.³ In addition to their use in treating depression and anxiety, antidepressants – in particular tricyclic anti-depressants – are also used to treat chronic pain disorders.^{5,6} The analgesic properties of the serotonin norepinephrine reuptake inhibitor (SNRI) class of antidepressants are being explored for the management of chronic pain and may offer another therapeutic option in the treatment of fibromyalgia.^{5,6}

The Technology

Milnacipran is an SNRI antidepressant that inhibits reuptake of both serotonin and norepinephrine.⁷ In vitro studies suggest that milnacipran has approximately equal influence on serotonin and norepinephrine.^{5,6} The

exact mechanism of its pain modulating effect is unknown; however, animal studies suggest that it is due to milnacipran's effect on serotonin and norepinephrine in the brain, spine, and peripheral sites.⁵

Regulatory Status

Cypress Bioscience Inc. and Forest Laboratories Inc. have joint North American marketing rights for milnacipran, but the drug is not currently licensed in either Canada or the US. The companies filed a new drug application with the US Food and Drug Administration (FDA) for milnacipran in fibromyalgia late in 2007.⁸ In Europe and Asia, milnacipran is licensed for the treatment of depression and is marketed under the brand names of Ixel, Dalcipran, Midalcipran, and Toledomin.⁹

Patient Group

Fibromyalgia is a chronic disease with no defined cause; the symptoms vary significantly over time but are rarely absent.³ According to the American College of Rheumatology (ACR), fibromyalgia is a disease of chronic generalized pain with at least 11 of 18 tender points on palpation. It is accompanied by fatigue, sleep disturbance, headache, irritable bowel syndrome, mood disorders, and other symptoms.^{10,11} It affects approximately 900,000 Canadians, with typical onset in early- to mid-adulthood, although it can develop in childhood.^{1,3}

Current Practice

The goal of fibromyalgia treatment is to reduce pain and improve physical and emotional function.^{1,3,12} A combination of pain-reducing medications, education about fibromyalgia, exercise, and evaluation and treatment of concurrent mood and sleep disorders is recommended for optimal management.^{3,12,13}

First-line medications shown to be effective for improving pain, sleep, fatigue, and overall well-being in clinical studies and in practice include low-dose tricyclic antidepressants (e.g., amitriptyline), or cyclobenzaprine.^{3,12,13} Other options

include serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants (e.g., venlafaxine), selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g., fluoxetine), and anti-convulsants (e.g., gabapentin and pregabalin).³ Acetaminophen and tramadol may be effective analgesics for fibromyalgia,³ but many of the other treatments currently in use are not consistently effective in reducing fibromyalgia pain.^{3,13}

The Evidence

Two published clinical trials of milnacipran in fibromyalgia and preliminary results of phase 3 studies (released in conference presentations) were identified.^{9,14-19} The two published trials were methodologically weak, and studies to date have not compared milnacipran to existing treatments for pain and other fibromyalgia symptoms.^{9,14,15} These short-term studies were hampered by patient withdrawal rates in excess of 25% in both the milnacipran and placebo groups.^{13,14,16,20} Complete phase 3 study results are not yet available, but initial reports from longer-term studies suggest that patient withdrawal from milnacipran continues at a high rate.^{16,17,19}

A 12-week multi-centre, phase 2 study in the US assessed the safety and analgesic efficacy of milnacipran in fibromyalgia.^{14,15} This study was placebo-controlled, randomized, and double-blind and included 125 patients without concurrent medical or psychiatric conditions. Ninety-eight percent of patients were women and the mean age was 47 years. Patients were taken off pre-existing centrally acting fibromyalgia medications before treatment began. Participants were randomized in a 2:3:3 ratio to receive placebo or milnacipran once daily or twice daily (initiated at 25 mg daily or 12.5 mg twice daily, with dose escalation to maximum tolerated dose or 200 mg per day over 4 weeks). Significant problems with the study design and clarity of reporting make the results of this study difficult to interpret. The primary pain outcome was the change in average daily pain score by electronic diary collection in the final two weeks compared to the baseline two-week results. A statistical analysis of this result was not reported. Secondary outcomes included the change from baseline in three different pain scales and five different disease rating scales. Only a few of these outcomes were reported in the published study. The reported pain score results demonstrated a large degree of variability and lack of statistical significance. The authors stated that the results of the secondary outcomes were not analyzed for the once-daily milnacipran patient group as they

found that twice-daily milnacipran was a more effective and better tolerated analgesic. Of the 35 patients (28%) who did not complete the study, 18 patients (including one patient in the placebo group) withdrew due to adverse events, and 17 patients withdrew for other reasons. The reported improvement in clinical global impression of change was 73% ($p=0.013$) with milnacipran twice daily, and 77% ($p=0.008$) with milnacipran once daily, compared to 38% with placebo for the 90 patients completing the study.^{14,15}

A 12-week, uncontrolled open-label study in Japan included 20 patients (17 women and three men) with fibromyalgia (according to ACR criteria) and concurrent depression.⁹ Milnacipran was administered starting at 15 mg twice daily and increased, according to physician preference, up to 100 mg daily. The final average dose of milnacipran was 59.7 mg per day. Pain, global condition, and depression were assessed at baseline and after 12 weeks. Two of the 20 patients withdrew due to persistent nausea. At the end of follow-up, five of the 20 patients had a greater than 50% reduction in pain and three of the 20 patients had a greater than 50% improvement in their global condition. Both outcomes were assessed using global visual analogue scales.

Preliminary pain and overall fibromyalgia symptom results of a three-month phase 3 study involving 1,196 patients were released by Forest Laboratories Inc. and Cypress Bioscience Inc. in 2007.^{16,17} The patient groups received milnacipran 100 mg per day, milnacipran 200 mg per day (dosing schedule not stated), or placebo. Withdrawal rates were 34%, 35%, and 28%, respectively. Specific outcome results for the 713 patients completing the study were not provided. However, the preliminary reports state that significantly more patients achieved at least a 30% improvement in pain, global impression of disease, and physical function with milnacipran (25% of patients on milnacipran 100 mg per day, $p=0.011$, and 26% of patients on 200 mg per day, $p=0.015$), compared with 13% of patients on placebo.^{16,17} Adverse effects and treatment failures led to early discontinuation of milnacipran in approximately 35% of patients.

Conference presentations summarize results from another trial involving 888 fibromyalgia patients who received milnacipran (100 mg or 200 mg per day) or placebo for up to one year.^{16,17,19} The patient withdrawal rate was 42% in the first six months of the study.¹⁷ Patients completing the first phase (six months) of the trial were eligible to continue in a subsequent re-randomization study. Of these 449 patients, 33% withdrew by the end of the first year.¹⁹ A recent conference abstract on the six-

month study reported statistically significant improvements in composite pain response rates for milnacipran 100 mg per day (50%) and milnacipran 200 mg per day (52%) versus placebo (33%).¹⁷ Full study results are not yet available.

Adverse Effects

Based on the published clinical trials,^{9,14,15} milnacipran's main adverse effects involve the gastrointestinal and cardiovascular systems.^{9,14,15} Gastrointestinal effects include nausea and abdominal pain; cardiovascular effects include increased heart rate and blood pressure, postural dizziness, and palpitations. Seventeen of the 18 patients in the phase 2 study who withdrew due to adverse effects were in the milnacipran treatment groups.¹⁴ Larger preliminary phase 3 study results report constipation, hot flushes, sweating, vomiting, palpitations, increased heart rate, increased blood pressure, dry mouth, and migraine in more than twice as many patients taking milnacipran compared with those receiving placebo.¹⁶ In patients treated with milnacipran (100 mg/day) for depression, reported adverse effects included nausea (11% of patients), dry mouth (8%), constipation (8%), and insomnia (6%).⁶ The incidence of adverse effects and high withdrawal rates in the initial studies in fibromyalgia suggest that tolerability may be dose-related and this may limit the use of milnacipran.

Antidepressant medications are associated with a potential risk of withdrawal reactions (e.g., anxiety, nausea), and serotonin syndrome.⁵ Serotonin syndrome is a rare condition characterized by mental status changes, neuromuscular abnormalities, and autonomic hyperactivity; its severity can range from benign to lethal. No cases of serotonin syndrome have been reported in the milnacipran trials to date.

Administration and Cost

Milnacipran is administered orally twice per day.^{5,7,21} The recommended dosage for depression is 50 mg twice daily, with dosage reduction in patients with impaired kidney function.²¹ The dosages used in fibromyalgia studies have been up to 200 mg per day. A Canadian cost for milnacipran is not yet available.

Concurrent Developments

In June 2007, pregabalin (Lyrica™) received US Food and Drug Administration (FDA) approval for the treatment of fibromyalgia.²² Pregabalin is licensed in Canada as an anti-convulsant and for the treatment of

neuropathic pain. Of note, 32% of fibromyalgia patients initially responding to pregabalin failed to sustain response with continued treatment.²² Duloxetine (Cymbalta®), a serotonin and norepinephrine reuptake inhibitor, was recently submitted to the FDA for the additional indication of fibromyalgia.²³ Duloxetine is not currently available in Canada. Clinical trials assessing several other drug treatments for fibromyalgia are also underway.¹³

Rate of Technology Diffusion

If milnacipran is approved for fibromyalgia in Canada, it may be an option for some patients who have not found relief from their symptoms with other medications. Available fibromyalgia treatments have not been particularly effective in reducing pain, improving disability, or sustaining compliance with the treatment;^{11,13} thus, there may be considerable interest in a new treatment option.

Implementation Issues

The diagnosis and treatment of fibromyalgia are problematic.³ Most patients manage their disease with a combination of medications, exercise, and other treatments. The cost-effectiveness of different treatment options has not been determined.²⁴ Fibromyalgia causes significant disability to patients in their productive years. Milnacipran may provide another alternative for pain and symptom relief in fibromyalgia for some patients; however, longer-term and comparative studies are needed. Existing studies of milnacipran included only a small number of men and further evidence of its efficacy in this patient group is also needed. Based on the limited clinical trial results to date, it is unclear if milnacipran will provide an advantage over existing treatment in terms of efficacy or fewer adverse effects. It is also unclear how safe and effective milnacipran will be as an adjunct to existing treatments and in patients with co-morbid conditions.

References

1. Murphy KA, et al. Fibromyalgia. In: *Health State Descriptions for Canadians: Musculoskeletal Diseases*. Ottawa: Statistics Canada; 2006. Available: <http://www.statcan.ca/english/research/82-619-MIE/2006003/fibromyalgia.htm>
2. McNally JD, et al. *Chronic Dis Can* 2006;27(1):9-16. Available: <http://www.phac-aspc.gc.ca/publicat/cdic-mcc/pdf/cdic271e.pdf>

3. Goldenberg DL. Treatment of fibromyalgia in adults. In: *UpToDate*. Version 15.2. [database online]. Waltham (MA): UpToDate; 2007.
4. Birtane M, et al. *Clin Rheumatol* 2007;26(5):679-84.
5. Leo RJ, et al. *Curr Opin Investig Drugs* 2006;7(7):637-42.
6. Stahl SM, et al. *CNS Spectr* 2005;10(9):732-47.
7. Puozzo C, et al. *Int Clin Psychopharmacol* 2002;17 Suppl 1:S25-S35.
8. *Forest and Cypress announce submission of new drug application for milnacipran for the treatment of fibromyalgia syndrome* [news release]. San Diego: Cypress Bioscience; 2007 Dec 31. Available: <http://www.cypressbio.com/news/releases/20071231.pdf>
9. Nagaoka S, et al. *Int J Psychiatry Clin Pract* 2004;8(1):47-51.
10. Mease PJ, et al. *J Rheumatol* 2005;32(11):2270-7.
11. Clauw DJ. *J Clin Rheumatol* 2007;13(2):102-9.
12. Rooks DS. *Curr Opin Rheumatol* 2007;19(2):111-7.
13. Goldenberg DL. *Best Pract Res Clin Rheumatol* 2007;21(3):499-511.
14. Gendreau RM, et al. *J Rheumatol* 2005;32(10):1975-85.
15. Vitton O, et al. *Hum Psychopharmacol* 2004;19(Suppl 1):S27-S35.
16. *Milnacipran demonstrated significant improvement in pain and the core symptoms of fibromyalgia syndrome, data show* [news release]. New York: Cypress Bioscience; 2007 Nov 8. Available: <http://www.cypressbio.com/news/releases/20071108.pdf>
17. Clauw DJ, et al. *Arthritis Rheum* 2007;56(Suppl 9):S306. Abstract no 716.
18. Clauw DJ, et al. Presentation at Annual Scientific Meeting of the American College of Rheumatology and the Association of Rheumatology Health Professionals; 2007 Nov 6; Boston (MA). Poster 517 (L1).
19. Goldberg D, et al. *Arthritis Rheum* 2007;56(Suppl 9):S603. Abstract no 1526.
20. *Forest Laboratories, Inc. and Cypress Bioscience, Inc. Announce Positive Results of Phase III Study for Milnacipran as a Treatment for Fibromyalgia Syndrome* [news release]. San Diego: Cypress Bioscience; 2007 May 22. Available: <http://ir.cypressbio.com/phoenix.zhtml?c=81458&p=irol-newsArticle&ID=1005672>
21. Milnacipran: International drug information. In: *UpToDate*. Version 15.2.[database online]. Waltham (MA): UpToDate; 2007.
22. Pregabalin (Lyrica) for fibromyalgia. *Med Lett Drugs Ther* 2007;49(1270):77-8.
23. *New Data Suggest Cymbalta® Reduced Pain in Fibromyalgia Patients With and Without Depression* [news release]. Indianapolis: Eli Lilly; 2007 Aug 21. Available: <http://newsroom.lilly.com/ReleaseDetail.cfm?ReleaseID=260556>
24. Robinson RL, et al. *Expert Opin Pharmacother* 2006;7(8):1027-39.

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