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MILNACIPRAN: A NEW AGENT FOR FIBROMYALGIA

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Fibromyalgia (FM) is often misunderstood and misdiagnosed with considerable socioeconomic effects on patients and society. Historically, treatment of this disease focused on correcting individual symptoms (depression, pain, sleep disturbances). Treatments included tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, tramadol, acetaminophen, pregabalin and gabapentin. In January of this year, milnacipran (Savella ®, a new selective serotonin and norepinephrine reuptake inhibitor (SNRI), was approved by the FDA for the treatment of FM. This article will describe the efficacy and safety profile of milnacipran compared to standard treatments in fibromyalgia.

ETIOLOGY

Fibromyalgia patients present with a constellation of symptoms and is the second most frequent presenting problem in rheumatology practices.[1] Fibromyalgia affects approximately 2-4% of the U.S. population (3.4% of women, 0.5% of men) and predominantly affects women in a ratio of 9:1 compared to men. Fibromyalgia is most prevalent in women ≥ 50 years; the rate of FM increases with age to a maximum prevalence of 7.4% in women aged 70 to 79 years.[2]

Research indicates that the socioeconomic impact of FM is immense. Between 15%-44% of the people with FM are receiving disability benefits and it is estimated that FM costs the American economy over $9 billion annually.[3]

The 1990 American College of Rheumatology classification criteria defined FM as history of widespread musculoskeletal pain that is present for ≥ 3 months with significant tenderness or pain in 11 of 18 point sites on digital palpation.[4]

Several causative mechanisms have been postulated to explain the abnormal pain perception. For instance, disturbed sleep has been implicated as a factor in FM pathogenesis. Nonrestorative sleep has been observed in most patients with FM. Sleep studies in patients with FM show disruption of normal stage 4 sleep (non–rapid eye movement sleep or NREM) by repeated α-wave intrusions. The idea that stage 4 sleep deprivation has a role in causing this disorder was supported by the observation that symptoms of fibromyalgia developed in normal subjects whose stage 4 sleep was disrupted artificially by induced α-wave intrusions.[3] Analyses of sleep electro-

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encephalographs (EEGs) demonstrate three types of sleep: phasic (50% of FM patients versus 7% of normal patients), tonic (20% of FM patients versus 9% of normal patients), and low (30% of FM patients versus 84% of normals).[5] Those with the phasic pattern of intrusion in slow-wave sleep (SWS) are more likely to have increased post-sleep tenderness and subjective pain, poor sleep efficiency, and less SWS than the other groups. Morning stiffness, diffuse pain, and discomfort after awakening commonly occur in FM patients with phasic sleep. Although a cause-effect relationship between pain and sleep cannot be established, the data suggest that the phasic sleep pattern is associated with longer duration of pain symptoms, perception of poor sleep, and morning pain. The finding of this EEG sleep disorder in children and their mothers suggests the possibility of a familial or genetic influence in the pathogenesis of the disorder.[5]

One key factor believed to cause abnormal pain perception is central pain, which is defined as enhanced nociceptive sensation caused by neural activities in the absence of peripheral input. This assertion is further supported by the lack of consistent peripheral abnormalities in patients with fibromyalgia.[6]

Biochemical studies of samples from patients with fibromyalgia have supported the notion that the pathology might be due to high levels of pronociceptive (i.e. increase sensitivity to pain) compounds, low levels of antinociceptive compounds, or both.[6]

The two principal descending antinociceptive pathways in humans are the opioidergic and mixed serotonergic–noradrenergic pathways. Current evidence suggests that the opioidergic systems might be maximally activated in individuals with fibromyalgia, as evidenced by high enkephalin levels noted in the CSF of fibromyalgia patients.[6] A decrease in descending antinociceptive activity is likely to occur because of deficiencies in the other antinociceptive pathway, the serotonergic–noradrenergic pathway. Studies show the principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene, is at a low level in the CSF of patients with fibromyalgia.[6] Similarly, there are data suggesting that patients with fibromyalgia have low levels of serotonin and its precursor, L-tryptophan in their serum, as well as reduced levels of the principal serotonin metabolite, 5-hydroxyindole acetic acid, in their CSF.

Many patients with FM have psychological abnormalities however there is disagreement as to whether these abnormalities represent reactions to the chronic pain or whether the symptoms of FM are a reflection of psychiatric disturbance. Approximately 30% of FM patients fit a psychiatric diagnosis, the most common being depression, anxiety, somatization, and hypochondriasis.[7] However, FM also occurs in patients without significant psychiatric problems.

PRESENTATION AND SEQUELAE

In FM patients, musculoskeletal and neurologic examinations are normal and there are usually no laboratory abnormalities. Symptoms are generalized musculoskeletal aching, stiffness, and fatigue. Patients may feel muscle pain after mild exertion, and some degree of pain is always present. The pain is described as a burning or gnawing pain or as soreness, stiffness, or aching. Patients awake frequently at night and have trouble falling back to sleep. Patients may experience cognitive impairment with difficulty thinking and loss of short-term memory. Headaches, including migraines, are also common.[7]

GENERAL TREATMENT OF FIBROMYALGIA

The initial step in treatment is to improve the quality of sleep. The use of TCAs (amitriptyline, nortriptyline, doxepin, or cyclobenzaprine) 1–2 h before bedtime will give the patient restorative sleep (stage 4), resulting in clinical improvement.[7] Patients should be started on a low dose and increased gradually as needed. Side effects of TCAs limit their use.
Depression and anxiety should be treated with appropriate drugs and, when indicated, with psychiatric counseling. Duloxetine, fluoxetine, sertraline, paroxetine, citalopram, or other SNRI and SSRIs can be used.[7] Other useful antidepressants include trazodone and venlafaxine. Alprazolam and lorazepam are effective for anxiety.[7]

For pain, duloxetine (Cymbalta®) and pregabalin (Lyrica®) are FDA approved to treat fibromyalgia pain; acetaminophen, tramadol, or gabapentin are also useful. Salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs) only partially improve symptoms and opiate analgesics should be avoided. Patients may benefit from regular low impact aerobic and stretching exercises, which are started after patients begin to have improved sleep and less pain and fatigue.[7]

MECHANISM OF ACTION

The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of FM in humans is unknown. However, milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake. Milnacipran inhibits norepinephrine uptake with approximately 3-fold higher potency in vitro than serotonin (5-HT) without directly affecting the uptake of dopamine or other neurotransmitters.

Acutely, milnacipran blocks 5-HT and NE reuptake into the neuron, increasing 5-HT and NE extracellular concentrations. This activates 5-HT and NE auto- and heteroreceptors culminating in a decrease in 5-HT and NE neuronal firing rates, synthesis, and release.[8] Chronically, milnacipran continues to block 5-HT and NE transporters without desensitization, but 5-HT and NE auto- and heteroreceptors are desensitized and thus, downregulated. Firing rates of 5-HT and NE return to normal, and the amount of 5-HT and NE released per nerve impulse is increased.[8]

Unlike SSRIs and TCAs, milnacipran has no significant affinity for α- and β-adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazepine, or γ-aminobutyric acid (GABA) receptors in vitro.[9] Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular side effects observed with other psychotropic drugs. Milnacipran has no significant affinity for Ca^{2+}, K^{+}, Na^{+} and Cl^{-} channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.[9]

PHARMACOKINETICS

Milnacipran is well absorbed after oral administration with an absolute bioavailability of approximately 85% to 90%; absorption is not affected by food. Milnacipran and its metabolites are excreted predominantly unchanged in urine (55%) with a terminal elimination half-life ($T_{1/2}$) of 6 to 8 hours.

Milnacipran achieves maximum blood concentrations (Cmax) within 2 to 4 hours post dose. The mean volume of distribution of milnacipran following a single IV dose in healthy subjects is approximately 400 L and plasma protein binding is 13%.[9] Milnacipran's excretion was evaluated following a single oral administration of 50 mg in mild (creatinine clearance [CLcr] 50-80 mL/min), moderate (CLcr 30-49 mL/min), and severe (CLcr 5-29 mL/min) renal impairment and in healthy subjects (CLcr > 80 mL/min). The mean area under the curve ($AUC_{0-\infty}$) increased by 16%, 52%, and 199%, and elimination half-life increased by 38%, 41%, and 122% in subjects with mild, moderate, and severe renal impairment, respectively, compared with healthy subjects.[9] No dosage adjustment is necessary for patients with mild renal impairment but caution should be exercised in moderate renal impairment. Dose adjustment is necessary in severe renal impairment patients.

Milnacipran's metabolism was evaluated following single oral administration of 50 mg in mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment and in healthy subjects. $AUC_{0-\infty}$ and $T_{1/2}$ were similar in healthy subjects and subjects with mild and moderate hepatic impairment. However, subjects with severe

Table 1. Fibromyalgia composite response at week 15.[1]

MEASURE	ANALYSIS TYPE	TREATMENT GROUP		
		Milnacipran 100 mg (%)	*Milnacipran 200 mg (%)*	*Placebo (%)*
≥ 30% improvement in PED-24h AM-recall pain	LOCF	149/399 (37.3)*	158/396 (39.9)†	115/401 (28.7)
	OC	124/237 (52.3)*	119/217 (54.8)†	101/263 (38.4)
PGIC ≤ 2	LOCF	138/399 (34.6)*	151/396(38.10) †	100/401 (24.9)
	OC	125/263 (47.5)†	129/255 (50.6)†	92/289 (31.8)
≥ 6 point increase from baseline in SF-36 PCS	LOCF	129/399 (32.3)‡	109/396 (27.5)	102/401 (25.4)
	OC	108/263 (41.1)*	89/255 (34.9)	86/290 (29.7)

PED = patient experience diary; LOCF=last observation carried forward; OC=observed cases; PGIC=patient global impression of change; SF-36=36-item short form health survey; PCS=physical component summary.

For comparisons to Placebo: *P≤ 0.01; †P≤ 0.001; ‡P< 0.05

hepatic impairment had a 31% higher $AUC_{0-\infty}$ and a 55% higher $T_{1/2}$ than healthy subjects. Caution should be exercised in patients with severe hepatic impairment.[9]

Compared to SSRIs, TCAs, and duloxetine, milnacipran has less risk for drug interactions involving the cytochrome P450 enzyme system. Neither milnacipran nor pregabalin induce or inhibit CYP enzymes, but duloxetine is metabolized by CYP 2D6 and 1A2 isoenzymes.

EFFICACY IN FIBROMYLAGIA

Several randomized, placebo-controlled trials have illustrated milnacipran's efficacy in treating FM and FM pain, but not sleep problems. Clauw and colleagues conducted a phase III, 15 week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial.[1] Of 2270 patients screened, 1196 patients were randomized to receive milnacipran 100mg/d (n = 399), milnacipran 200mg/d (n = 396), or placebo (n = 401). The primary endpoints were rates of FM composite responders and rates of FM pain composite responders. FM composite responders were defined as patients experiencing concurrent changes in the following domains: pain (≥ 30% improvement from baseline in the morning-recall visual analog scale [VAS] pain score), patients' global status (a Patient Global Impression of Change [PGIC] rating of 'very much improved' or 'much improved' at week 15), and physical function (a ≥ 6-point improvement on the 36-item Short-Form Health Survey [SF-36] Physical Component Summary score). FM pain composite responders were defined as those who met the pain and PGIC criteria. The majority of patients were female (96.2%) and white (93.5%), with an mean age of 50.2 years, baseline weight of 180.8 lbs, and baseline body mass index of 30.6 kg/m^2. There were no significant differences in baseline demographic and clinical characteristic between the 3 treatment arms.

Compared with placebo, a significantly greater proportions of milnacipran-treated patients were FM composite responders (100 mg/d: $P = 0.01$; 200 mg/d: $P = 0.02$) and FM pain composite responders (100 mg/d: $P = 0.03$; 200 mg/d: $P = 0.004$) as described in Table 1. Milnacipran was associated with significant improvements in pain after 1 week of treatment (100 mg/d: $P = 0.004$; 200 mg/d: $P = 0.04$), as well as significant improvements in multiple secondary efficacy end points, including global status (PGIC: $P<0.001$ for both doses), physical function (SF-36 physical functioning domain—100 mg/d: $P < 0.001$; 200 mg/d: $P = 0.02$), and fatigue (Multidimensional Fatigue Inventory— 100 mg/d: $P = 0.04$). A significant reduction in pain was observed as early as 1 week after the start of double-blind treatment in both milnacipran arms compared to placebo. Maximal pain relief was achieved within 9 weeks and was maintained throughout the study.[1]

The Medical Outcomes Study (MOS) sleep problems Index II evaluated changes from baseline in sleep between patients on 100 mg/d, 200 mg/d, or placebo. No significant change from baseline was seen in patients taking 100 mg and 200 mg versus placebo.[1]

Table 2. Fibromyalgia composite response at 15 and 27 weeks.[10]

MEASUREMENT	15 WEEKS			27 WEEKS		
	Placebo (n=223)	*Milnacipran 100mg* (n=224)	*Milnacipran 200mg* (n=441)	*Placebo* (n=223)	*Milnacipran 100mg* (n=224)	*Milnacipran 200mg* (n=441)
Fibromyalgia						
BOCF/LOCF %	12.1	19.6 (0.028)	19.3 (0.017)	13%	18.3 (0.245)	18.1 (0.105)
Observed cases %	17.3	32.8 (0.003)	32.8 (<0.001)	19.4%	33.3 (0.056)	31.9 (0.017)
Fibromyalgia pain						
BOCF/LOCF %	19.3	27.2 (0.056)	26.8 (0.032)	18.4%	25.9 (0.072)	25.6 (0.034)
Observed cases %	27.2	45.2 (0.003)	45.4 (<0.001)	27.9%	43.8 (0.021)	45.2 (0.001)

BOCF=baseline observation carried forward; LOCF= last observation carried forward.
Data in ( )'s represent p-value compared to placebo.

Table 3. Depression trials involving milnacipran vs. SSRIs.

TRIAL	COMPARATOR	SCALE	SAMPLE SIZE	DURATION (WEEKS)	SIGNIFICANT DIFFERENCE	COMMENTS
Clerc, *et al.*[14] *(*2001)	Fluvoxamine	HAMD	113	6	No (p=0.05)	Milnacipran trended toward > reduction in HAMD score
Sechter, *et al.*[13] *(*2004)	Paroxetine	HAMD	302	6	No (p=0.85)	
Lee, *et al.*[12] *(*2005)	Fluoxetine	HAMD	70	6	No (p>0.05)	Small sample size, Asian population, short duration

Mease and colleagues, conducted a 27-week, randomized, double-blind, multicenter study comparing milnacipran at doses of 100 and 200 mg to placebo.[10] The two primary endpoints were rates of FM responders and FM pain responders (concurrently satisfied response criteria for pain, PGIC, and SF-36). Composite responder rates are presented in Table 2. The percentage of patients who met the criteria as FM composite responders was significantly higher with both doses of milnacipran compared to placebo [15 weeks: placebo = 17.3%, 200 mg/d = 32.8% ($p< 0.001$), 100 mg/d = 32.8% ($p< 0.003$); and 27 weeks: placebo = 19.4%, 200 mg/d = 31.9% ($p = 0.017$), 100 mg/d = 33.3% ($p = 0.056$)]. Similarly, the proportion of patients meeting criteria as FM pain composite responders was significantly higher with milnacipran compared to placebo at 15 and 27 weeks. No difference was noted between placebo and milnacipran treatment in terms of quality or quantity of sleep as measured by the MOS-Sleep Problems Indices.[10]

Recent studies in depressed patients have suggested that newer drugs like milnacipran, which enhance NE and 5HT neurotransmission, result in higher response and remission rates than the SSRIs; however these findings contrast a meta-analysis that found no significant differences in antidepressant efficacy.[11]

A variety of head to head trials have compared milnacipran to an SSRI to determine milnacipran's efficacy in depression. Lee and colleagues, compared milnacipran to fluoxetine in 70 patients for 6 weeks. Both treatments produced a significant decrease in Hamilton Depression Scale (HAM-D) score, but no significant difference was found between the two treatment groups.[12] However, these findings are limited by methodological flaws, including a small sample size, high drop out rate, and unbalanced depression history at baseline. Sechter et al, compared milnacipran to paroxetine in 302 patients for 6 weeks and found a significant decrease in average HAM-D scores with both milnacipran and paroxetine. However, the two groups were not statistically different from each other.[13] Clerc and colleagues, compared milnacipran to fluvoxamine in 113 patients for 6 weeks. Milnacipran showed greater reduction in HAM-D scores (62.1% vs. 49.3%) but the difference did not reach statistical significance.[14] Overall, milnacipran has shown similar or greater efficacy than SSRIs in treating depression and depressive symptoms (Table 3).

ADVERSE EFFECTS

Table 4 summarizes the most frequently reported adverse events (frequency ≥ 5% of patients in either milnacipran treatment group and at an incidence rate≥ twice that of placebo).[10] Most frequently reported adverse events were nausea, headache and constipation. Although the absolute rates of occur-

Table 4. Percentage of trial subjects experiencing adverse effects.[10]

ADVERSE EVENT	PLACEBO	MILNACIPRAN 100 MG/DAY	MILNACIPRAN 200 MG/DAY
Nausea	21.1	32.6	40.1
Headache	11.7	15.6	17.7
Constipation	2.7	18.3	14.3
Hyperhidrosis	2.2	9.8	12.5
Dizziness	6.7	11.6	11.3
Hot Flush	2.7	9.8	10.4
Insomnia	6.7	10.7	9.3
Vomiting	1.8	4.9	8.2
Sinusitis	8.1	4.9	7.3
Tachycardia	2.2	5.4	7.3
Dry mouth	2.7	5.8	7.0
URTI	7.2	8.9	6.8
Palpitations	0.9	8.0	5.7
Diarrhea	7.2	4.5	5.2

rence were small, palpitations tachycardia, and blood pressure increases occurred at least twice as much in the milnacipran groups than placebo.[9]

Adverse events resulted in the premature discontinuation of 10.3%, 19.6%, and 27.0% of placebo and milnacipran 100 and 200 mg/day patients, respectively.[10] The discontinuation rates of milnacipran are similar to the discontinuation rates of placebo and other FDA approved FM drugs.[15,16] Contraindications include the use of monoamine oxidase inhibitors concomitantly or uncontrolled narrow-angle glaucoma.[9] Since milnacipran has very little muscarinic, histaminergic, or adrenergic activities, it exhibits a better safety profile compared with TCAs and at least a similar, if not better, safety profile when compared to SSRIs.[8]

COST

The most commonly studied milnacipran dose is 50 mg twice daily. A one month supply of such a dose of Savella® costs approximately $119.99.[17]

SUMMARY

Milnacipran is effective in FM, FM pain, and depression but has shown no efficacy in treating sleep disturbances in FM. Its greatest advantage over duloxetine is its low risk for pharmacokinetic drug interactions. This is especially important for FM patients who may be on other medications for sleep problems or depression. An important advantage over pregabalin is milnacipran's weight neutrality. Milnacipran can cause GI problems (nausea, constipation) and cardiovascular issues (tachycardia, hypertension), but its greatest disadvantage may be its price.

♦ ♦ ♦

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