Effects Of Milnacipran On Sleep And Pain In Subjects With Fibromyalgia

Ahmed M[1], Aamir R[1], Jishi Z[1], Scharf MB[1]

[1]Cleveland Sleep Research Center, Middleburg Heights, OH, USA

Abstract Number: 0881
Poster Number: 223

Introduction

- Fibromyalgia (FM) is a chronic pain disorder considered to impact an estimated 5 to 6 million Americans with the vast majority of complainants female.
- FM is characterized by widespread pain and tenderness, pervasive fatigue, cognitive impairment and complaints of non-restorative sleep.
- Alpha intrusion into sleep has been found to be very common in subjects with light and fragmented sleep.
- Milnacipran, a selective serotonin norepinephrine inhibitor with weak binding affinity for the N-Methyl-D-aspartate (NMDA) receptor received the US Food and Drug Administration (FDA) approval for the management of FM.
- This study examined the effects of milnacipran on polysomnographic (PSG) measures of sleep and subjective complaints in fibromyalgia subjects with disturbed sleep.

Methods

- This was a single site randomized, double-blind, placebo-controlled, 2-period crossover PSG study.
- Eligible subjects (age 28-72 years) were randomized (1:1) to milnacipran (100 mg/day) or placebo for crossover period 1, and vice versa for period 2. Each crossover period comprised a dose-escalation and dose-maintenance phase, with a 2-week taper/washout between periods.
- In-laboratory PSGs were collected at baseline, and at the end of each treatment period. The primary endpoints were the difference in PSG-recorded wake after sleep onset (WASO), number of awakenings after sleep onset (NAASO), and sleep efficiency (SE) between 4 weeks of maintenance treatment with milnacipran and placebo.
- Other PSG endpoints were latency to persistent sleep (LPS), total sleep time (TST), arousal index (AI), and slow wave sleep (SWS) as a percent of total sleep time.

Results

Subjects
- Subjects were predominately women (17 [89.5%] of 19), white (17 [89.5%] of 19) with a mean age of 49.2 years (range 28–72 years) and a mean weight of 196.7 lbs (n= 19; ± 54.0). The mean duration of FM was 9.2 years (n=18; ± 6.9) and the mean years since diagnosis of FM was 4.2 (n=17; ± 5.1).
- Of 19 subjects randomized, 15 completed both treatment periods.

Efficacy
- Subjects treated with milnacipran showed no significant improvements in WASO and NAASO, but showed reduced SE (p=0.049) (Table 1).
- Milnacipran did not show significant changes in other PSG parameters.
- Milnacipran treatment did not result in statistically significant differences from placebo in any of the subjective scales (Table 1).
- Two thirds of completers met responder criteria and additionally showed a significant improvement in daily pain interference (p= 0.043) and subjective sleep quality (p=0.040) (Table 2).

Tolerability
- No drug related SAEs were observed in the study. The incidence of treatment emergent adverse events was 64.2% in subjects treated with milnacipran compared to 35.7% in subjects treated with placebo. The AEs were mostly mild to moderate with nausea/vomiting and headache being the most commonly reported.

Table 1. PSG parameters and symptoms of FM subjects at baseline and after 4-week maintenance treatment with milnacipran and placebo.

	Baseline* Mean (SD)	Milnacipran Mean (SE)	Placebo Mean (SE)	Paired difference (95% CI)	*t_{19} (p-value)
Objective PSG parameters					
WASO, minutes	97.2 ± 70.6	76.2 (10.8)	53.6 (8.1)	22.6 (-0.6, 45.8)	2.086 (0.056)
NAASO	31.9 ± 12.9	39.5 (4.5)	34.9 (4.2)	4.6 (-7.3, 16.6)	0.824 (0.424)
Sleep efficiency %	72.3 ± 15.8	77.1 (3.8)	83.3 (2.3)	-6.1 (-12.2, -0.04)	-2.159 (0.049)[£]
LPS, min	49.4 ± 43.4	41.6 (6.2)	38.6 (5.8)	3.0 (-12.5, 18.5)	0.416 (0.683)
TST, min	340.7 ± 78.9	361.7 (19.6)	386.1 (12.5)	-24.4 (-59.1, 10.4)	-1.502 (0.155)
Arousal index [/hr]	24.8 ± 9.8	30.2 (2.2)	31.2 (4.0)	-1.0 (-9.8, 7.8)	-0.252 (0.805)
SWS, % of TST	4.2 ± 8.4	8.4 (2.7)	9.4 (2.6)	-1.0 (-11.6, 9.6)	-0.200 (0.844)
Subjective symptoms					
Sleep problem index 2 (MOS-SS)	55.6 ± 14.4	37.8 (4.4)	34.9 (3.8)	2.9 (-6.4, 12.2)	0.677 (0.509)
Sleep quality scale	4.1 ± 1.6	5.2 (0.52)	4.9 (0.40)	0.32 (-0.3, 0.6)	1.076 (0.300)
FSS total score	50.4 ± 10.6	41.0 (3.4)	42.3 (3.1)	-103 (-8.2, 5.6)	-0.414 (0.685)
FIQ total score	56.7 ± 12.6	40.0 (6.8)	45.3 (4.0)	-5.3 (-17.0, 6.4)	-0.970 (0.349)
BPI mean severity score	5.4 ± 1.2	4.1 (0.6)	4.7 (0.4)	-0.6 (-1.8, 5.6)	-1.065 (0.305)
BPI mean interference score	6.4 ± 1.5	3.8 (0.6)	4.3 (0.5)	-0.5 (-1.8, 0.8)	-0.821 (0.425)

*t and p-values are based on paired t-test comparison between milnacipran and placebo. All analyses were performed on the per-protocol population (n=15) that completed the study taking 100 mg/day of milnacipran or matching placebo. 95% CI = 95% confidence interval of the difference; higher paired difference values and positive paired difference values indicate improved sleep. [£] significant at 0.05 level.

Table 2. BPI interference scores and sleep quality for responders at the end of the treatment period with milnacipran and placebo (n= 10)

	Milnacipran Mean (SE)	Placebo Mean (SE)	Paired difference (95% CI)	t_9 (p-value)
BPI pain interference	2.59 (0.56)	4.03 (0.58)	-1.44(-2.83, -0.05)	-2.350(0.043)*
Sleep quality scale	5.34 (0.61)	4.70(0.52)	0.64(0.04, 1.24)	2.396(0.040)*

*Significant at 0.05 level. BPI = Brief pain inventory; 95% CI= 95% confidence interval of the difference.

Discussion

- Responder analysis showed a significant improvement in subjective sleep quality based on daily sleep diaries.
- The reduction in pain seems to be due to the analgesic effect of milnacipran in these subjects and any sleep benefit is an indirect consequence.
- Norepinephrine and serotonin contribute to pain and sleep modulation, the higher NE reuptake activity may account for the lack of sedation.
- Milnacipran has been shown to increase orexinergic transmission in the hypothalamus and histaminic transmission in the frontal cortex. Both of these neurotransmitters may also contribute to wakefulness.

Table 3. Summary of reported treatment-emergent adverse events in each treatment group. Data are number (%) of subjects.

Adverse event	Milnacipran 100mg/day(n =18)	Placebo (n =18)
Nausea/vomiting	4 (22.2)	0
Headache	3 (16.7)	0
Abdominal pain	2 (11.1)	3 (16.7)
Constipation	2 (11.1)	2 (11.1
Sinusitis	2 (11.8)	1 (5.6)
Hot flush	2 (11.8)	0
Cold/flu	1 (5.6)	2 (11.8)
Dry mouth	1 (5.6)	1 (5.6)
Increased heart rate	1 (5.6)	0
Increased perspiration	1 (5.6)	0
Cold sweats	1 (5.6)	0
Excessive menstrual bleeding	1 (5.6)	0
Abnormal ejaculation	1 (5.6)	0
Excessive urination	1 (5.6)	0
Pruritus	1 (5.6)	0
Petechial rash	1 (5.6)	0
Periodontal disease	1 (5.6)	0
Foot sprain	1 (5.6)	0
Worsening of pain	0	2 (11.8)
Streptococcal sore throat	0	1 (5.6)
Increased blood pressure	0	1 (5.6)
Diarrhea	0	1 (5.6)
Gallstones	0	1 (5.6)

Conclusion

- The data suggests that milnacipran is not sedating in most subjects with fibromyalgia.
- Improvements in sleep are likely a result of improvement in pain.

References

[1] Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain 1996;68;363-8.

[2] Harding SM. Sleep in fibromyalgia subjects: subjective and objective findings. Am J Med Sci 1998;315:367–376.

[3] Clauw DJ, Mease P, Palmer RH, Gendreau M, Wang Y. Milnaciprin for the treatment of fibromyalgia in adults: A 15-week, multicenter, randomized, double-blind, placebo-controlled, multi-dose clinical trial. Clin Therap 2008;30(11):1988-2004.

[4] Mease PJ, Clauw DJ, Gendreau RM, Srinivas GR, Kranzler J, Wei-Chen, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. J. Rheumatol 36, 398-409, 2009.

[5] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. NIH Publication. No. 204. Washington, DC: U.S. Government Printing Office, 1968.

[6] Iber C, Ancoli-Israel S, Chesson AL, Jr., Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.

[7] Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol: Clin Exp 2004;19(supp):27-35.

[8] Vaikshnavi SN, Nemeroff CB, Plott SJ, Rao SG, Kranzler J, Owens MJ. Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. Biol Psychiatry 2004;55:320-2.

[9] Rahmadi M, Narita M, Yamashita A, Imai S, Kuzumaki N, Suzuki T. Sleep disturbance associated with an enhanced orexinergic system induced by chronic treatment with paroxetine and milacipran. Synapse, 2011 7;652-657.

Acknowledgement

The study was supported by Forest Research Institute, Jersey City, NJ 07311-4994