Drug Use Research & Management Program
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New Drug Review: Milnacipran (Savella®)

INDICATIONS

Milnacipran is approved by the FDA for the management of fibromyalgia only.[1] Fibromyalgia is not a covered Oregon Health Plan diagnosis.

Possible off-label indications of milnacipran include: treatment of major depressive disorders, anxiety disorders, panic disorders, management of neuropathic pain, obsessive-compulsive disorders, ADHD, and stress incontinence.

BACKGROUND

Milnacipran is a selective norepinephrine and serotonin reuptake inhibitor (SNRI). It was originally developed and manufactured (in 1997) in France as an antidepressant. Forest Laboratories has worked with the original manufacturer in development of milnacipran for the treatment of fibromyalgia.

There are currently three medications with an FDA indication for fibromyalgia: milnacipran (Savella), duloxetine (Cymbalta), and pregabalin (Lyrica). Duloxetine and milnacipran are pharmacologically similar and are both SNRIs. Although these are the only FDA approved pharmacologic therapies, TCAs, SSRI/SNRIs, analgesics and anti-anxiety medications have shown efficacy in clinical trials and are often used in therapy. A 2008 systematic review of antidepressants, including milnacipran, in the treatment of fibromyalgia found no evidence of superiority of one class of antidepressant over another.[2]

The EULAR (European League Against Rheumatism) and American Pain Society (APS) management of fibromyalgia guidelines indicate effective therapy is a combination of education, pharmacologic and non-pharmacologic treatments.[3,4] EULAR guidelines recommend use of amitriptyline, fluoxetine, duloxetine, milnacipran, pregabalin or tramadol (level of evidence Ib), in combination with non-pharmacologic therapy to reduce pain. Systematic reviews indicate amitriptyline has the strongest evidence of efficacy as a result of being the most studied, however no distinction is made among efficacy of first line agents due to a lack of head-to-head trials.[2,5] Pharmacologic treatment should be chosen based on patient preference, comorbidities, and previous treatments as well as specific drug characteristics and side effect profiles.

CLINICAL PHARMACOLOGY

The exact mechanism of how milnacipran confers its ability to improve symptoms of fibromyalgia is unknown. Milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake.[1] These actions are postulated to improve multiple fibromyalgia symptoms such as peripheral and central pain, depressiveness, sleep and quality of life.

CLINICAL EFFICACY

Efficacy was evaluated in 3 randomized, double-blind, placebo control trials. The length of these trials ranged from 12-27 weeks of treatment. The trials included patients age 18-70 years with a current diagnosis of fibromyalgia, the majority (>95%) of whom were females. [6-8] Treatment doses were50mg BID and 100mg BID in the Clauw and Mease trial and a range of 25mg/d to 200mg/d in the Gendreau trial. Doses were titrated over 2-4 weeks to minimize side effects and improve tolerability.

Primary endpoints from the two pivotal trials were: [6-8]

- Composite response rates for fibromyalgia as a whole
  - ≥30% improvement in VAS pain score
  - PGIC (patient global impression of change) rating of much improved or very improved
  - and ≥ 6 point improvement in SF-36 PCS score
- Composite response rates for pain
  - ≥30% improvement in VAS pain score
  - PGIC (patient global impression of change) rating of much improved or very improved

Multiple secondary outcomes assessed the individual components of the primary composite endpoints with numerous evaluation tools.

Table 1. Responder Rates Summary

TRIAL	COMPOSITE RESPONDER RATES (P-VALUE)		PAIN COMPOSITE ENDPOINT (P-VALUE)	
Gendreau	NSS		NSS	
Mease	15 weeks	27 weeks	15 weeks	27 weeks
100mg	19.6% (0.028)	18.3% (NS)	27.2% (NS)	25.9% (NS)
200mg	19.3% (0.017)	18.1% (NS)	26.8% (0.032)	25.6% (0.034)
placebo	12.1%	13.0%	19.3%	
	15 weeks		15 weeks	
Clauw				
100mg	15% (<0.05)		23% (<0.05)	
200mg	14% (<0.05)		25% (<0.01)	
placebo	9%		16%	

The Gendreau trial presented no significant results for the primary endpoints.[8] However, this trial did establish that BID dosing showed a more positive trend in terms of efficacy and safety compared to QD and thus was the basis for later trials dosing schemes.

At 15 weeks, the Mease trial found an ARR of 7.5% (NNT = 13) and 7.2% (NNT = 14) for the 100mg and 200mg treatment groups when evaluating composite responder rates. However, this significant effect was lost at 27 weeks for both strengths. The 200mg dose revealed an ARR of 7.2% (NNT = 13) and 7.5% (NNT = 14) at 15 and 27 weeks for the pain composite endpoint compared to placebo. Interestingly, the 100mg dose was non-significant at both evaluation periods.[7]

In the Clauw trial, composite responder rate was significant at both strengths, ARR of 6% (NNT = 17) and 5% (NNT = 20) for the 100mg and 200mg respectively. The trial also demonstrated significance for pain composite responder rates, ARR of 7% (NNT = 14) and 9% (NNT = 11) for the 100mg and 200mg dose.[6]

While studies demonstrated milnacipran is efficacious according to the composite endpoints, the individual components, particularly pain reduction, did not demonstrate statistical significance in post-hoc analyses.

DRUG SAFETY AND ADVERSE EFFECTS

General Summary: Adverse effects are generally reported as mild to moderate and decreasing over continued therapy. Most common adverse effect include: nausea, headache and constipation.[1]

Discontinuation due to adverse events from the trials occurred most frequently with milnacipran 200 mg/day (24%), followed by 100 mg/day (19%) and then the placebo group (9%). The NNH is 7-10. Most frequent adverse events that caused discontinuation were: nausea, palpitations, depression, increased heart rate, constipation and headache.[4] Overall, milnacipran was reasonably well tolerated and side effect pattern appears comparable to duloxetine.

Possible serious adverse events with milnacipran treatment were primarily cardiac (increases in HR and BP) in nature and occurred infrequently. Other serious adverse events include serotonin syndrome, increased blood pressure, increased heart rate, seizures, hepatotoxicity, hyponatremia, abnormal bleeding, activation of mania and dysuria.[1]

Unanswered Safety Concerns: Longer term data is needed to identify appropriate use in patients with significant comorbid conditions, especially CVD and psychiatric conditions.

COST INFORMATION

Medication	Recommended Dose	Cost/30 Days
Savella	50 mg bid	$122*
Cymbalta	60 mg daily	$128*
Lyrica	150 mg bid	$150*
fluoxetine	20 mg qam	$5**
amitriptyline	25 mg qhs	$1**
cyclobenzaprine	10 mg qhs	$2**
venlafaxine IR	75 mg daily	$26**
tramadol	50 mg qid	$22**

* Cost from Medispan as of April 15, 2009 for AWP (minus 15%) for brand products.
** MAC prices from Oregon Medicaid were used for generics (March 2009).

SUMMARY AND RECOMMENDATIONS:

- Fibromyalgia response rates with milnacipran are modest at best. The NNT is approximately 13 by week 15, but effectiveness with chronic use is questionable.
- Currently available systematic reviews do not identify advantages over other antidepressants. Further comparative studies are needed to clarify if differences exist.
- Milnacipran's side effect profile is similar to other agents within its class.
- Prior authorization criteria should be established to reflect its limited use under the Oregon Health Plan.

REFERENCES

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