

## Cochrane Corner



## Are serotonin and noradrenaline reuptake inhibitors effective, tolerable, and safe for adults with fibromyalgia? A Cochrane Review summary with commentary

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The aim of this commentary is to discuss the recently published Cochrane Review "Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia" by Welsch et al.<sup>1</sup>, under the direct supervision of Cochrane Pain, Palliative and Supportive Care Group. This Cochrane Corner is produced in agreement with the Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation.

**Background:** Despite better understanding of the pathogenesis of fibromyalgia, this condition still represents a challenge for both health professionals dealing with it as well as for patients who suffer. Fibromyalgia is diagnosed if pain is present in at least four of five regions (4 quadrants + axial) with similar level of symptoms persisting for at least three months along with widespread pain index (WPI) being equal to or greater than 7 and symptom severity scale (SSI) score being equal to or greater than 5 or WPI of 4-6 and SSI score being equal to or greater than 9 and the diagnosis being valid irrespective of other diagnosis according to the revised 2010/2011 American College of Rheumatology criteria<sup>2</sup>. People with fibromyalgia complain not only about chronic debilitating widespread pain but also fatigue, sleep problems and frequent depressive episodes. Numerous

problems in functioning including activity limitations and participation restrictions result in significant disability and reduced health related quality of life (HRQoL) in individuals with fibromyalgia<sup>3,4</sup>. At this stage, there is no specific cure for fibromyalgia patients. Treatment includes both pharmacological and nonpharmacological modalities. All these modalities aim to relieve the symptoms and to improve HRQoL. Among medications, serotonin and noradrenaline reuptake inhibitors (SNRIs) are widely used; however, EULAR revised guideline for fibromyalgia 2017 (evaluating only duloxetine and milnacipran) provides a weak recommendation for their use due to their relatively small effects on pain, sleep and disability and no or little effects on fatigue<sup>5</sup>. Therefore, more recent evidence is significant for the possible change in the recommendation of SNRIs. A recent Cochrane review (Welsch et al., 2018) approached SNRIs comprehensively for the treatment of fibromyalgia in adults, evaluating desvenlafaxine and venlafaxine in addition to duloxetine and milnacipran, and looked at various outcomes for SNRIs including pain, patient global Impression, fatigue, sleep problems, HRQoL as well as tolerability and safety.

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<sup>1</sup> The abstract/plain language summary of this Cochrane Review is taken from a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2018, Issue 2, DOI: 10.1002/14651858.CD010292.pub2. (see [www.cochranelibrary.com](http://www.cochranelibrary.com) for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.



## Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia (Welsch et al., 2018)

### What is the aim of the Cochrane review?

The aim of this Cochrane Review is to show the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or another active comparator in the treatment of fibromyalgia in adults.

### What was studied in the Cochrane review?

The population addressed in this review was 7903 adults with fibromyalgia from eighteen studies. The interventions included seven studies which investigated duloxetine and nine studies which investigated milnacipran against placebo. One study compared desvenlafaxine versus placebo and pregabalin and one study compared duloxetine versus L-carnitine. The outcomes studied includes: pain relief of 50% or greater and of 30% or greater, patient's global impression, fatigue, sleep problems, health-related quality of life, mean pain intensity, depression, anxiety, disability, sexual function, cognitive disturbances and tenderness.

### Search methodology and up-to-dateness is of the Cochrane review

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the US National Institutes of Health and the WHO International Clinical Trials Registry Platform as well as the reference lists of reviewed articles were searched for relevant studies up to 8 August 2017.

### What are the main results of the Cochrane review?

The review included eighteen studies with a total of 7903 adults diagnosed with fibromyalgia.

The review shows that:

- The SNRIs duloxetine and milnacipran had a clinically relevant benefit over placebo in patient-perceived global improvement which much or very much improved in 52% of those receiving the intervention compared to 29% of those on placebo.
- Duloxetine and milnacipran also showed a clinically relevant benefit over placebo in patient-reported pain relief of 30% and greater, but no clinically relevant benefit for pain relief of 50% or greater. However, duloxetine and milnacipran showed clinically relevant benefit over placebo in reducing mean pain intensity, tenderness, and disability. Desvenlafaxine did not show superiority over placebo in reducing mean pain intensity.
- Duloxetine and milnacipran showed no clinically relevant benefit when compared to placebo in reducing fatigue and depression and in improving HRQoL and cognitive disturbances.
- No differences between duloxetine or milnacipran and placebo in reducing problems in sleep or anxiety.
- No difference between desvenlafaxine and placebo (based

on one small study) or duloxetine and desvenlafaxine (based on two studies using L-carnitine or pregabalin as active comparators) in terms of effectiveness, safety and tolerability.

- No differences in between duloxetine, milnacipran or desvenlafaxine and placebo regarding serious adverse events.

### How did the authors conclude on the evidence?

The authors concluded that that the SNRIs duloxetine and milnacipran provided no clinically relevant benefit when compared to placebo for a pain relief of 50% or greater and in reducing fatigue and in improving HRQoL. A clinically relevant benefit existed in terms of pain relief of 30% or greater and in much or very much improvement of patient's global impression. There was no significant difference between these drugs and placebo in reducing problems in sleep. The quality of evidence was low or very low for all comparisons of studied SNRIs either with placebo or with other active medications as well as for adverse events due to concerns of publication bias, indirectness, or imprecision. The dropout rates were higher for duloxetine and milnacipran than for placebo due to adverse events. Generally, the potential benefits of these drugs were outweighed by their potential harms. A minority of persons with fibromyalgia might benefit substantially from duloxetine or milnacipran in terms of symptom relief and good tolerability.

### What are the implications of the Cochrane evidence for clinical practice and research?

The review authors make the following inferences from the evidence for clinical practice and research persons with fibromyalgia (Welsch et al., 2018):

- For the patients: SNRIs duloxetine and milnacipran may produce meaningful relief of symptoms and well tolerability in only a minority of persons with fibromyalgia and not in the majority with the possibility of discontinuation of these medications due to lack of substantial benefit on symptoms and/or adverse events.
- For physicians: If physicians consider duloxetine or milnacipran for treatment, it is important that they discuss with their patients the potential benefits and harms of these medications as well as the contraindications including abundant use of alcohol, use of monoamine oxidase inhibitors concomitantly, narrow-angle glaucoma which is uncontrolled, or chronic liver damage. Warnings need to be done for possible unwanted conditions such as serotonin or discontinuation syndrome, increase in blood pressure, abnormal bleeding, urinary retention, hepatotoxicity, and suicidality. It is also recommended that realistic goals of treatment are defined together with the patients before starting treatment.
- For policy-makers: The minority of persons with fibromyalgia who benefit from these medications may be considered sufficiently valuable provided that

appropriate switching or discontinuation of treatment are well considered.

- For funders: The evidence that some persons with fibromyalgia benefit from duloxetine and milnacipran may be considered worthwhile in consideration of appropriate rules for stopping and switching as well as supervision by an experienced physician in the use of these medications.

**Recommendations for research by the authors of the Cochrane Review** (Welsch et al., 2018) are:

- The availability of participant-level data.
- The need for studies worldwide and inclusion of persons with comorbidities for external validity.
- The identification of comorbid anxiety and depressive disorders at the onset of studies for stratification.
- Proper details and reporting of adverse events.
- Control for potential effects of individual interventions on outcomes in the case of combined interventions.
- The use of responder criteria in relation to fatigue, sleep problems, depression and disability as measurement of endpoints.

**Remaining issues:** From a rehabilitation perspective, it is also important to assess the effects of SNRIs on activities and participation in major life areas as defined in the International Classification of Functioning, Disability and Health<sup>6</sup>. Among these, studying return-to-work outcomes relevant to SNRIs merits specific attention.

#### Acknowledgements

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