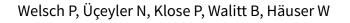


Cochrane Database of Systematic Reviews

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia (Review)



Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD010292. DOI: 10.1002/14651858.CD010292.pub2.

www.cochranelibrary.com



[Intervention Review]

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia

Patrick Welsch¹, Nurcan Üceyler², Petra Klose³, Brian Walitt⁴, Winfried Häuser⁵

¹Health Care Center for Pain Medicine and Mental Health, Saarbrücken, Germany. ²Department of Neurology, University of Würzburg, Würzburg, Germany. ³Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany. ⁴National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA. ⁵Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany

Contact: Winfried Häuser, whaeuser@klinikum-saarbruecken.de.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2020.

Citation: Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD010292. DOI: 10.1002/14651858.CD010292.pub2.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Fibromyalgia is a clinically defined chronic condition of unknown etiology characterized by chronic widespread pain that often co-exists with sleep disturbances, cognitive dysfunction and fatigue. People with fibromyalgia often report high disability levels and poor quality of life. Drug therapy, for example, with serotonin and noradrenaline reuptake inhibitors (SNRIs), focuses on reducing key symptoms and improving quality of life. This review updates and extends the 2013 version of this systematic review.

Objectives

To assess the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

Search methods

For this update we searched CENTRAL, MEDLINE, Embase, the US National Institutes of Health and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials and examined the reference lists of reviewed articles, to 8 August 2017.

Selection criteria

We selected randomized, controlled trials of any formulation of SNRIs against placebo or any other active treatment of fibromyalgia in adults.

Data collection and analysis

Three review authors independently extracted data, examined study quality, and assessed risk of bias. For efficacy, we calculated the number needed to treat for an additional beneficial outcome (NNTB) for pain relief of 50% or greater and of 30% or greater, patient's global impression to be much or very much improved, dropout rates due to lack of efficacy, and the standardized mean differences (SMD) for fatigue, sleep problems, health-related quality of life, mean pain intensity, depression, anxiety, disability, sexual function, cognitive disturbances and tenderness. For tolerability we calculated number needed to treat for an additional harmful outcome (NNTH) for withdrawals due to adverse events and for nausea, insomnia and somnolence as specific adverse events. For safety we calculated NNTH for serious adverse events. We undertook meta-analysis using a random-effects model. We assessed the evidence using GRADE and created a 'Summary of findings' table.



Main results

We added eight new studies with 1979 participants for a total of 18 included studies with 7903 participants. Seven studies investigated duloxetine and nine studies investigated milnacipran against placebo. One study compared desvenlafaxine with placebo and pregabalin. One study compared duloxetine with L-carnitine. The majority of studies were at unclear or high risk of bias in three to five domains.

The quality of evidence of all comparisons of desvenlafaxine, duloxetine and milnacipran versus placebo in studies with a parallel design was low due to concerns about publication bias and indirectness, and very low for serious adverse events due to concerns about publication bias, imprecision and indirectness. The quality of evidence of all comparisons of duloxetine and desvenlafaxine with other active drugs was very low due to concerns about publication bias, imprecision and indirectness.

Duloxetine and milnacipran had no clinically relevant benefit over placebo for pain relief of 50% or greater: 1274 of 4104 (31%) on duloxetine and milnacipran reported pain relief of 50% or greater compared to 591 of 2814 (21%) participants on placebo (risk difference (RD) 0.09, 95% confidence interval (CI) 0.07 to 0.11; NNTB 11, 95% CI 9 to 14). Duloxetine and milnacipran had a clinically relevant benefit over placebo in patient's global impression to be much or very much improved: 888 of 1710 (52%) on duloxetine and milnacipran (RD 0.19, 95% CI 0.12 to 0.26; NNTB 5, 95% CI 4 to 8) reported to be much or very much improved compared to 354 of 1208 (29%) of participants on placebo. Duloxetine and milnacipran had a clinically relevant benefit compared to placebo for pain relief of 30% or greater. RD was 0.10; 95% CI 0.08 to 0.12; NNTB 10, 95% CI 8 to 12. Duloxetine and milnacipran had no clinically relevant benefit for fatigue (SMD -0.13, 95% CI -0.18 to -0.08; NNTB 18, 95% CI 12 to 29), compared to placebo. There were no differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD -0.07; 95 % CI -0.15 to 0.01). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in improving health-related quality of life (SMD -0.20, 95% CI -0.25 to -0.15; NNTB 11, 95% CI 8 to 14).

There were 794 of 4166 (19%) participants on SNRIs who dropped out due to adverse events compared to 292 of 2863 (10%) of participants on placebo (RD 0.07, 95% CI 0.04 to 0.10; NNTH 14, 95% CI 10 to 25). There was no difference in serious adverse events between either duloxetine, milnacipran or desvenlafaxine and placebo (RD -0.00, 95% CI -0.01 to 0.00).

There was no difference between desvenlafaxine and placebo in efficacy, tolerability and safety in one small trial.

There was no difference between duloxetine and desvenlafaxine in efficacy, tolerability and safety in two trials with active comparators (L-carnitine, pregabalin).

Authors' conclusions

The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran.

We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran.

PLAIN LANGUAGE SUMMARY

Serotonin and noradrenaline reuptake inhibitors for fibromyalgia

Bottom line

Duloxetine and milnacipran may reduce pain in people with fibromyalgia. However, some of these people may also experience side effects, such as nausea (feeling sick) and drowsiness. A minority of people with fibromyalgia experience symptom relief without side effects from duloxetine and milnacipran.

Background

People with fibromyalgia often have chronic (longer than three months) widespread pain, as well as problems with sleep, thinking and exhaustion. They often report poor health-related quality of life. There is no cure for fibromyalgia at present, so the treatments aim to relieve the symptoms and to improve health-related quality of life.

Serotonin and noradrenaline are chemicals which are produced by the human body, involved in the regulation of pain, sleep and mood. Low concentrations of serotonin have been reported in people with fibromyalgia. Serotonin and noradrenaline reuptake inhibitors (SNRIs) are a class of antidepressants that increase the concentration of serotonin and noradrenaline in the brain.

Study characteristics



In August 2017, we updated our searches for clinical trials in which SNRIs were used to treat symptoms of fibromyalgia in adults. We found eight new studies since the previous version of the review. In total, we found 18 studies with 7903 participants. The studies were four to 27 weeks long and compared the SNRIs desvenlafaxine, duloxetine and milnacipran against a fake medication (placebo). We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results.

Key results and quality of the evidence

Duloxetine and milnacipran were better than placebo in reducing pain by 50% or more and in improving global well-being (low-quality evidence). Duloxetine and milnacipran were better than placebo in improving health-related quality of life and in reducing fatigue (low-quality evidence). Duloxetine and milnacipran were not better than placebo in reducing sleep problems (low-quality evidence). More people dropped out of the trial due to side effects with duloxetine and milnacipran than with placebo (low-quality evidence). More people reported nausea and drowsiness with duloxetine and milnacipran than with placebo (low-quality evidence). Duloxetine, milnacipran and placebo did not differ in the frequency of serious side effects experienced (very low-quality evidence).