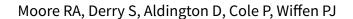


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# Amitriptyline for neuropathic pain and fibromyalgia in adults (Review)



Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ.

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#### [Intervention Review]

# Amitriptyline for neuropathic pain and fibromyalgia in adults

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#### **ABSTRACT**

#### **Background**

Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and is recommended in many guidelines. These types of pain can be treated with antidepressant drugs in doses below those at which the drugs act as antidepressants.

# **Objectives**

To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia. To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia.

#### **Search methods**

We searched CENTRAL, MEDLINE, and EMBASE to September 2012, together with reference lists of retrieved papers, previous systematic reviews, and other reviews; we also used our own handsearched database for older studies.

#### **Selection criteria**

We included randomised, double-blind studies of at least four weeks' duration comparing amitriptyline with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

# **Data collection and analysis**

We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants in the comparison. The second tier used data that failed to meet this standard and were therefore subject to potential bias.

# Main results

Twenty-one studies (1437 participants) were included; they individually involved between 15 and 235 participants, only four involved over 100 participants, and the median study size was 44 participants. The median duration was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common.

There was no top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia.



Second-tier evidence indicated no evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain, and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals; 8/153 (5%) withdrew because of lack of efficacy with amitriptyline and 14/119 (12%) with placebo.

More participants experienced at least one adverse event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5 (95% CI 1.4 to 1.7) and the number needed to treat to harm was 4.1 (95% CI 3.2 to 5.7). Adverse event and all-cause withdrawals were not different.

### **Authors' conclusions**

Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all.

It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy.

## PLAIN LANGUAGE SUMMARY

#### Amitriptyline for neuropathic pain and fibromyalgia in adults

The review set out to examine how well amitriptyline worked in treating neuropathic pain or fibromyalgia, where the definition of worked involved both a high level of pain relief and the ability to take the tablets over a longer time without side effects being intolerable. There were no studies that could provide an answer that was trustworthy or reliable, because most studies were relatively old, and used methods or reported results that we now recognise as making benefits seem better than they are. This is disappointing, but we can still make useful comments about the drug.

Amitriptyline probably does not work in neuropathic pain associated with HIV or treatments for cancer. Amitriptyline probably does work in other types of neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, and post-stroke pain, and in fibromyalgia), though we cannot be certain of this. Our best guess is that amitriptyline provides pain relief in about 1 in 4 (25%) more people than does placebo, and about 1 in 4 (25%) more people than placebo report having at least one adverse event, probably not serious but disconcerting; we cannot trust either figure based on the information available.

The most important message is that amitriptyline probably does give really good pain relief to some patients with neuropathic pain or fibromyalgia, but only a minority of them; amitriptyline will not work for most people.