

# Amitriptyline

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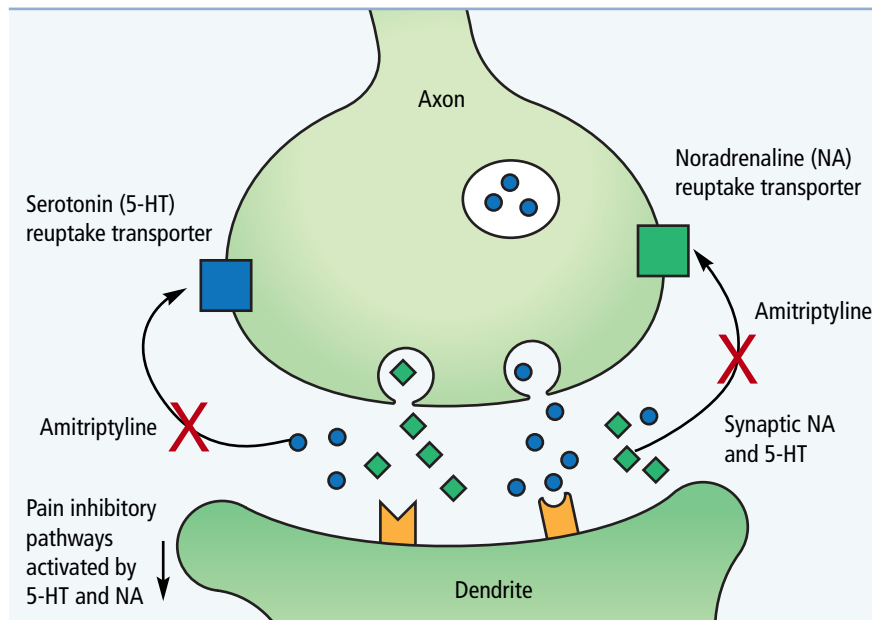


Figure 1. Pharmacological action of amitriptyline

## Introduction

Painful diabetic neuropathy affects up to a third of people with diabetes mellitus. Unfortunately, it is difficult to treat, being unresponsive to conventional analgesics. Amitriptyline, a tricyclic antidepressant, has been used for its analgesic properties in the treatment of diabetic neuropathy since 1977, although is not licensed for this indication. It features on the WHO Model List of Essential Medicines and has also shown benefit in the management of fibromyalgia, nocturnal enuresis and migraine.

## Pharmacology

Amitriptyline was the second tricyclic antidepressant to be synthesised by Merck in 1960 after imipramine. Its main action is to increase activity of serotonergic and noradrenergic neurones by inhibiting central serotonin and noradrenaline reuptake at the synapse, but has much lesser effect on dopamine (Figure 1). It exhibits further blockade at adrenergic ( $\alpha_1$ ), histaminergic (H<sub>1</sub>), muscarinic (mCh) and NMDA receptor sites, as well as sodium and L-type calcium channels, leading to many potential unintended and toxic clinical effects.

Amitriptyline undergoes extensive first-pass metabolism in the liver through the cytochrome p450 enzymes CYP2D6 and CYP2C19 to nortriptyline, which has additional clinical effects. Amitriptyline is more potent at the serotonin receptor, while nortriptyline has greater action on noradrenaline. Amitriptyline has 45% bioavailability and is tightly protein bound in plasma. It is largely renally excreted in conjugated forms but does not require dose adjustment in renal impairment.

Its mechanism as an antidepressant is thought to be through increasing central serotonin levels. The analgesic effect is less well understood. One theory is that serotonin and noradrenaline are involved in blocking descending spinal cord pain pathways; however, amitriptyline is analgesic at lower doses and in faster time than it achieves antidepressant activity, which does not support a central amine effect. Additionally, there has not been a documented change in mood in studies of patients achieving an analgesic benefit.

The use of amitriptyline is partly limited by concern over side effects. Sedation is common and it is usually prescribed at night to avoid this. Antimuscarinic effects include dry

eyes, postural hypotension, glaucoma, constipation, confusion and urinary retention. Other potential effects are hypersensitivity, akathisia, mania and cardiac arrhythmia. Concerns have been raised about a small increased risk of suicidal ideation in children and young people treated with this drug. It is also contraindicated post myocardial infarction.

Amitriptyline is potentially lethal in overdose, hence its decline in treatment of psychiatric disorders. The main concerns are of cardiac toxicity through cardiac sodium channel blockade and serotonin syndrome.

There are multiple drug interactions which should be taken into account when prescribing the drug, particularly with those which augment the cytochrome P450 system, monoamine oxidase inhibitors and cisapride (as it can potentiate QTc prolongation).

### Trials of safety and efficacy

A 2015 Cochrane review of evidence for use of amitriptyline in neuropathic pain found only 15 randomised control trials between 1988 and 2015 with suitable design methodology to include in their review.<sup>1</sup> All were randomised, double-blinded and concerned pain of at least moderate severity. No trial met criteria for first or second tier evidence, meaning that at best only an indication of beneficial effect could be drawn. The studies were criticised for being small and of short duration, and had unclear outcomes meaning evidence was biased in favour.

The overall conclusion was that amitriptyline may have some efficacy in treating neuropathic pain, except cancer and HIV associated pain. The NNT for a 'significant benefit' versus placebo was 5.1.

### Specific evidence for use in diabetes

Five of the 15 aforementioned trials specifically concerned painful diabetic neuropathy. They compared amitriptyline to pregabalin, topical capsaicin, duloxetine or pregabalin, lamotrigine or desipramine, fluoxetine and placebo.

One trial was a partially randomised, two-phase, cross-over trial which compared responses of patients with at least moderate

painful diabetic neuropathy to desipramine and amitriptyline in one group, with fluoxetine and placebo (bentropine) in the other.<sup>2</sup> The patients received six weeks of one drug, followed by a wash-out period of two weeks, then a further six weeks of the second drug. It was rationalised that because measurements were taken on the sixth week, the wash-out time was actually extended further. Seventy-nine patients were initially assigned to either the desipramine/amitriptyline study or the fluoxetine/placebo study – 57 were randomly assigned in double-blinded fashion, but those with a known contraindication were knowingly assigned to the other. After completion, 29 subsequently crossed over to the alternate trial. Overall, 38 patients completed the amitriptyline/desipramine study, and 48 completed the fluoxetine/placebo study. Doses were escalated as tolerated throughout the study and varied widely in the tricyclic arm (from 12.5–150mg). Both amitriptyline and desipramine were effective in reducing pain to a similar degree and regardless of whether the patient was clinically depressed (74% vs 71% achieved at least a moderate reduction in pain respectively). Fluoxetine, as expected, was no better than placebo at 48%. Seven of the total 54 patients taking amitriptyline withdrew because of side effects. A similar withdrawal rate was seen with desipramine, but less with fluoxetine and placebo. In fact, 71% reported a dose-limiting side effect with amitriptyline, the most common being dry mouth and fatigue.

Another small, randomised control trial of 83 patients compared amitriptyline, pregabalin and duloxetine at increasing doses over a four-week period.<sup>3</sup> Ten patients withdrew due to adverse effects – only one from the amitriptyline group – and a further eight were not accounted for. Amitriptyline was commenced at 25mg bd, increasing to 25mg am, 50mg nocte after two weeks. Duloxetine was increased from 60mg od to 60mg bd, and pregabalin from 150mg bd to 300mg bd. The trial found no statistical difference between the pain response to any agent, as measured by the Brief Pain Inventory. Pregabalin reduced

### Key points

- Amitriptyline is a tricyclic antidepressant widely used for neuropathic pain
- Evidence is lacking as to its efficacy but it is still recommended as a first-line agent by NICE
- Prescribers should use amitriptyline with care in the elderly and in those at risk of self-harm due to significant side effects and lethality in overdose

pain score from 3.1 to 2.4, duloxetine from 3.4 to 2.2, and amitriptyline from 3.5 to 2.6. Secondary endpoints included analysis of sleep behaviour, quality of life and cognitive function. Duloxetine was found to impair sleep while pregabalin improved it, and there was no significant change in quality of life or cognitive function. All three drugs were well tolerated in this study.

The overall conclusion from the Cochrane review was that there was no difference between amitriptyline and the other interventions.<sup>1</sup>

### Discussion

Despite poor quality evidence, years of experience have led NICE to amend its recommendations for the management of neuropathic pain, now recommending that amitriptyline, pregabalin, gabapentin or duloxetine can all be used as first-line drugs (except in trigeminal neuralgia).<sup>4</sup> Amitriptyline has an obvious cost advantage over the others. The risk of cardiac toxicity, potential for serious effects in overdose, and risk of drug interactions should all be borne in mind by the prescriber.

### Declaration of interests

There are no conflicts of interest declared.

### References

1. Moore RA, et al. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev* 2015;(7): CD008242.
2. Max MB, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326(19):1250–6.
3. Boyle J, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care* 2012;35(12):2451–8.
4. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. (CG173). NICE, 2013.