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[Intervention Review]

Pharmacologic interventions for treating phantom limb pain

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 12, 2011. Phantom limb pain (PLP) is pain that arises in the missing limb after amputation and can be severe, intractable, and disabling. Various medications have been studied in the treatment of phantom pain. There is currently uncertainty in the optimal pharmacologic management of PLP.

Objectives

This review aimed to summarise the evidence of effectiveness of pharmacologic interventions in treating PLP.

Search methods

For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and Embase for relevant studies. We ran the searches for the original review in September 2011 and subsequent searches for this update up to April 2016. We sought additional studies from clinical trials databases and reference lists of retrieved papers.

Selection criteria

We included randomised and quasi-randomised trials studying the effectiveness of pharmacologic interventions compared with placebo, another active treatment, or no treatment, in established PLP. We considered the following outcomes: change in pain intensity, function, sleep, depression or mood, quality of life, adverse events, treatment satisfaction, and withdrawals from the study.

Data collection and analysis

We independently assessed issues of study quality and extracted efficacy and adverse event data. Due to the wide variability in the studies, we did not perform a meta-analysis for all the interventions and outcomes, but attempted to pool the results of some studies where possible. We prepared a qualitative description and narrative summary of results. We assessed clinical heterogeneity by making qualitative comparisons of the populations, interventions, outcomes/outcome measures, and methods.

Main results

We added only one new study with 14 participants to this updated review. We included a 14 studies (10 with low risk of bias and 4 with unclear risk of bias overall) with a total of 269 participants. We added another drug class, botulinum neurotoxins (BoNTs), in particular botulinum toxin A (BoNT/A), to the group of medications reviewed previously. Our primary outcome was change in pain

intensity. Most studies did not report our secondary outcomes of sleep, depression or mood, quality of life, treatment satisfaction, or withdrawals from the study.

BoNT/A did not improve phantom limb pain intensity during the six months of follow-up compared with lidocaine/methylprednisolone.

Compared with placebo, morphine (oral and intravenous) was effective in decreasing pain intensity in the short term with reported adverse events being constipation, sedation, tiredness, dizziness, sweating, voiding difficulty, vertigo, itching, and respiratory problems.

The N-methyl D-aspartate (NMDA) receptor antagonists ketamine (versus placebo; versus calcitonin) and dextromethorphan (versus placebo), but not memantine, had analgesic effects. The adverse events of ketamine were more serious than placebo and calcitonin and included loss of consciousness, sedation, hallucinations, hearing and position impairment, and insobriety.

The results for gabapentin in terms of pain relief were conflicting, but combining the results favoured treatment group (gabapentin) over control group (placebo) (mean difference -1.16, 95% confidence interval -1.94 to -0.38; 2 studies). However, gabapentin did not improve function, depression score, or sleep quality. Adverse events experienced were somnolence, dizziness, headache, and nausea.

Compared with an active control benztropine mesylate, amitriptyline was not effective in PLP, with dry mouth and dizziness as the most frequent adverse events based on one study.

The findings for calcitonin (versus placebo; versus ketamine) and local anaesthetics (versus placebo) were variable. Adverse events of calcitonin were headache, vertigo, drowsiness, nausea, vomiting, and hot and cold flushes. Most of the studies were limited by their small sample sizes.

Authors' conclusions

Since the last version of this review, we identified another study that added another form of medical therapy, BoNTs, specifically BoNT/A, to the list of pharmacologic interventions being reviewed for clinical efficacy in phantom limb pain. However, the results of this study did not substantially change the main conclusions. The short- and long-term effectiveness of BoNT/A, opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anaesthetics for clinically relevant outcomes including pain, function, mood, sleep, quality of life, treatment satisfaction, and adverse events remain unclear. Based on a small study, BoNT/A (versus lidocaine/methylprednisolone) does not decrease phantom limb pain. Morphine, gabapentin, and ketamine demonstrate favourable short-term analgesic efficacy compared with placebo. Memantine and amitriptyline may not be effective for PLP. However, results must be interpreted with caution, as they were based mostly on a small number of studies with limited sample sizes that varied considerably and also lacked long-term efficacy and safety outcomes. The direction of efficacy of calcitonin, local anaesthetics, and dextromethorphan needs further clarification. Overall, the efficacy evidence for the reviewed medications is thus far inconclusive. Larger and more rigorous randomised controlled trials are needed for us to reach more definitive conclusions about which medications would be useful for clinical practice.

PLAIN LANGUAGE SUMMARY

Drugs to treat phantom limb pain in people with missing limbs

Background

People can experience pain in a missing body part, for example after limb amputation. This is known as phantom limb pain. Various medications have been tried as treatments for phantom limb pain. It is uncertain whether any of the following medications work: botulinum toxin A, opioids, N-methyl D-aspartate (NMDA) receptor antagonists (e.g. ketamine, memantine, dextromethorphan), anticonvulsants, antidepressants, calcitonin, and local anaesthetics. It is unclear whether these medications can help with pain, function, mood, sleep, quality of life, treatment satisfaction, and safety (e.g. adverse events) in the short and long term.

Key results

For this updated review, we repeated the search for relevant clinical trials in April 2016. We found one new trial, including 14 studies with a total of 269 participants. One small initial report showed that botulinum toxin A did not reduce phantom limb pain compared to lidocaine/methylprednisolone. Morphine, gabapentin, and ketamine provided short-term pain relief compared with placebo, but the findings were mostly based on small studies. The results for calcitonin (versus placebo; versus ketamine) and local anaesthetics (versus placebo) were variable. The trials were very different, which made it difficult to combine results for the different drugs. Most studies

did not report sleep, depression or mood, quality of life, satisfaction with treatment, or the number of people who did not finish the study.

As they relied on a few small studies, results must be interpreted with caution. There was not enough information about long-term effectiveness and safety. Large, good-quality studies with longer follow-ups and outcomes that are important to patients are needed. Bigger and better studies will help us to make firmer conclusions on the best pain relief available for these patients.