A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain

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CRD summary
The review concluded that at least three classes of oral analgesics were effective for neuropathic pain: antidepressants, opioids and gabapentinoids. Multimodal treatment and combining drugs with different action modes may provide more effective treatment for neuropathic pain and required further research. The reliability of the authors’ conclusions is unclear due to potential limitations in the review process and limited evidence.

Authors' objectives
To evaluate the safety and efficacy of oral analgesics in neuropathic pain in head-to-head randomised controlled trials.

Searching
MEDLINE and The Cochrane Library were searched from 1966 to 2009 for publications in English. Search terms were reported. The US Food and Drug Administration website was searched. Bibliographies of retrieved articles and systematic reviews of oral analgesics (antidepressants, anticonvulsants, opioids and cannabinoids) in chronic non-cancer neuropathic pain were handsearched.

Study selection
Head-to-head RCTs that evaluated the safety and efficacy of oral analgesics for chronic non-cancer neuropathic pain in adults were eligible for inclusion. Only trials with a Jadad quality score of at least 3 were included. Trials that compared topical agents, intravenous studies, trials of acute neuropathic pain conditions, neuropathic pain with cancer and neuropathic pain conditions of trigeminal neuralgia and complex regional pain syndrome were excluded. The main outcome was pain relief. Other relevant outcomes were quality of life and vitality scores.

Sixty-three per cent of trials compared different types of analgesics, sometimes in combination. Included analgesics were opioids, a benzodiazepine, gabapentinoids, a phenothiazine, a cannabinoid, sodium channel-blocking agents, antidepressants including tricyclic antidepressants, a selective serotonin/norepinephrine reuptake inhibitor and lamotrigine. Other trials compared different drugs of the same class, all antidepressants. Tricyclic antidepressants, a tetracyclic antidepressant, a serotonergic drug, selective serotonin reuptake inhibitors (SSRI), mianserin and venlafaxine were included. Regimes were reported. Two thirds of the trials had a placebo control. Seventy per cent of studies were of patients with postherpetic neuralgia and/or painful diabetic neuropathy; patients in other studies had post-amputation pain, HIV neuropathy, lumbar root pain and chronic sciatica, spinal cord injury and chronic neuropathic pain. Pain duration ranged from more than two weeks to 20 years.

The authors did not report how many reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed using the Jadad scale of randomisation blinding, withdrawals and drop-outs. Studies with a Jadad quality score of at least 3 out of 5 were included.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
The percentage of patients with moderate or greater pain relief was extracted for each intervention, with the significance of the result. The percentage of patients with more than 50% improvement, number needed to treat (NNT), number needed to harm (NNH) and number needed to quit (NNQ), were extracted.

The authors did not report how many reviewers performed data extraction.
Methods of synthesis
A narrative synthesis was provided.

Results of the review
Twenty-seven RCTs were identified (2,082 participants, range 11 to 338). Twenty-one trials had a crossover design. Six trials were of parallel design. Five RCTs had a Jadad score of 3, 11 RCTs scored 4, 10 RCTs scored 5 and the Jadad score was not reported for one RCT. Nineteen studies included a placebo control.

Pain relief: There was no significant benefit over other analgesics in reducing neuropathic pain for benzodiazepine lorazepam (one RCT), phenothiazine fluphenazine (one RCT), sodium channel-blocking agents, mexiletine (one RCT) and carbamazepine (one RCT). Gabapentinoids pregabalin (one RCT) and gabapentin (two RCTs) were not significantly more effective than tricyclic antidepressants (amitriptyline (AT)) and significantly less effective in two RCTs. Two studies found non-significant trends for opioids (morphine, methadone) to be superior to tricyclic antidepressants (amitriptyline) and gabapentinoids (gabapentin).

Comparisons of antidepressants: Tricyclic antidepressants did not significantly differ in their pain-reducing efficacy (amitriptyline, nortriptyline, desipramine and imipramine). Noradrenergic desipramine was at least as effective as amitriptyline in reducing pain (two RCTs). Tetracyclic maprotiline was significantly less effective in reducing pain than amitriptyline (two RCTs). Mianserin did not significantly reduce pain compared to placebo in one RCT where imipramine was significantly effective. Three small lower-quality studies found that the serotonergic drug clomipramine was significantly more effective in reducing pain than imipramine and desipramine, and imipramine was significantly more effective than the SSRI paroxetine. There was poor evidence for the effectiveness of the SSRI fluoxetine (one RCT with no significant effect and one RCT with a low but significant effect compared to desipramine and amitriptyline, which were more effective). Imipramine was more effective than venlafaxine in reducing pain in one RCT, but the difference was not significant. There was evidence for individual variability in responsiveness when individual antidepressants were compared in three RCTs. The authors concluded that noradrenergic and nonadrenergic/serotonergic tricyclic antidepressants were more effective for neuropathic pain.

There appeared to be no greater benefit for the use of newer drugs (gabapentin, venlafaxine, pregabalin and lamotrigine). Results for other outcomes were reported: patient's global indicator of change (PGIC), present pain index (PPI), overall activity, vitality scores, pain-related interference in daily activity, short form 36 health survey (SF-36), quality of life and adverse events. Little data were reported for adverse events.

Authors' conclusions
The review identified important information about the relative efficacy and safety of drugs in different categories and within a category. Some significant differences between active treatments were reported. Comparative RCTs indicated efficacy within three broad classes of agents for neuropathic pain: antidepressants, opioids and gabapentinoids.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions and study design. The main outcome (pain relief) was clearly described, but other outcomes were not. Relevant databases were searched for studies published in English and so some relevant studies may have been missed. Unpublished studies were considered. Publication bias was not assessed. Study quality was assessed using suitable criteria and only studies of adequate quality were included. Although 27 studies were identified, many of the included studies were small and many different drugs were investigated. The authors did not report whether they made efforts to reduce error and bias in the review process. Relevant study details were reported. There were no details of age and gender of participants. The narrative synthesis was extensive, presumably due to the heterogeneity of the interventions.

Individual authors had received research support from or collaborated in trials with various pharmaceutical companies or held an intellectual property licensed to EpiCept (USA). One of the included studies was industry sponsored.

The authors did not make clear overall conclusions. Potential limitations that arose from the review process made the reliability of the conclusions unclear.
Implications of the review for practice and research

**Practice:** The authors suggested that multimodal treatment and combinations of different drugs with different modes of action may provide more effective treatment for neuropathic pain. Trial and error use of different antidepressants was suggested as different patients may respond to one antidepressant and not another.

**Research:** The authors identified a need for more and improved head-to-head RCTs to inform clinical choices. RCTs should include combinations of drugs. Head-to-head trials without a placebo may require more power. Newer more expensive drugs should be evaluated carefully alongside established drugs for efficacy and safety. RCTs should follow Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines.

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