Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: a systematic review

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CRD summary

This review found little evidence available on the treatment of refractory neuropathic pain with pregabalin, lidocaine plasters and duloxetine. The authors' cautious conclusions regarding the evidence from the uncontrolled studies in the review are likely to be reliable.

Authors' objectives

To assess the efficacy, safety and tolerability of pregabalin, lidocaine plasters and duloxetine in patients with refractory neuropathic pain.

Searching

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1998 to December 2008 for relevant studies published in English. Search terms were provided as additional material to the review. Abstracts from 11 conferences from 2004 to 2008 were handsearched to identify additional studies. OpenSIGLE and Google Scholar were searched.

Study selection

Studies of patients with refractory central or peripheral neuropathic pain due to any cause or lower back pain with a neuropathic component who were treated with pregabalin, lidocaine plaster or duloxetine as monotherapy or in combination were eligible for inclusion. Any design except case series designs, any comparator and studies that enrolled mixed populations of refractory and non-refractory patients were included.

The included patients presented various neuropathies and pain syndromes. These included diabetic peripheral neuropathy, trigeminal neuralgia, low back pain, radiculopathy, complex regional pain syndrome, neuropathic cancer pain and restless leg syndrome with neuropathic pain. Therapies administered previously included gabapentin, trycyclics, anti-depressants and anticonvulsants. Where reported, various concomitant medications were taken by the patients. Pregabalin was given at a range of doses that ranged from 50 to 600mg/day. Lidocaine plasters were typically administered with up to four plasters of lidocaine 5% to the painful areas. Gabapentin was administered at doses that ranged from 150 to 300mg. Duloxetine was given at doses from 60 to 120mg/day. Outcomes evaluated were reductions in pain and outcomes related to quality of life, safety and tolerability.

Two reviewers independently performed the study selection. Any discrepancies between the reviewers were resolved by a third reviewer.

Assessment of study quality

Methodological quality was assessed using a scale to assess quality components in terms of reporting of question and the inclusion criteria, presence of bias (losses to follow-up, patient recruitment, randomisation, blinding, completeness/length of follow-up and identification of confounding effects) and usefulness of the study.

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

Data extraction

Data on efficacy, safety and tolerability outcomes as reported in the included studies were extracted by two independent reviewers. Any disagreements were resolved by a third reviewer.

Methods of synthesis

Results were summarised in a narrative synthesis supported by tables. The authors stated that inconsistency in reported outcomes and a paucity of statistical data precluded a quantitative meta-analysis.

Results of the review

Seventeen studies (622 participants) were included in the review. Nine studies evaluated pregabalin. Seven studies evaluated use of lidocaine plasters. One study summarised an active controlled study of duloxetine (18 participants). Withdrawals were reported in seven pregabalin trials (5% to 30%) and four lidocaine plaster studies (6% to 11%), but not in the study of duloxetine. Most of the included studies were single-arm trials. One randomised controlled trial of lidocaine plasters was included in which lidocaine plasters were compared to placebo plasters. Follow-up across the studies ranged from four weeks to 18 months.

Use of pregabalin (nine studies, 422 participants) was associated with statistically significant reductions in pain intensity (all nine studies) and complete pain relief achieved by 25% of patients. The proportion of patients who reported at least 50% reductions in pain ranged from 33% to 49%. A range of 26% to 46% did not respond to pregabalin medication at all. Significant improvements with the administration of pregabalin were observed in one study each in overall quality of life, function interference, sleep interference, interference associated with mood, daily activities and pain-associated distress. One study showed that more than 60% of patients were satisfied with pregabalin treatment. Adverse events associated with pregabalin treatment were dizziness (16% to 66% of patients) and somnolence (15% to 40% of the patients). Withdrawals due to adverse events ranged from 5.5% to 14.3%.

Use of lidocaine plasters was investigated by seven studies (182 participants), one of which was a randomised controlled trial. One of the three studies that reported efficacy outcomes with the use of lidocaine plasters reported statistically significant reductions in pain. Between 13% and 22% of patients reported complete pain relief with application of lidocaine plasters. Adverse events included application site reactions or papules (4% to 28%) and local erythema (14% to 15%). Withdrawals due to adverse events ranged from 2.8% to 8.5%.

One trial of duloxetine in patients with trigeminal neuralgia found that pain severity was significantly reduced after 12 weeks compared to baseline. No safety or tolerability data were reported for duloxetine on specific adverse events or withdrawals.

Authors' conclusions

Little evidence was available on the treatment of refractory neuropathic pain with pregabalin, lidocaine plasters and duloxetine. There was a lack of high-quality comparative studies and definitions of refractory neuropathic pain were inconsistent.

CRD commentary

The review addressed a defined question. Criteria for the inclusion of studies were broad in scope. Appropriate electronic databases were searched. Attempts were made to identify unpublished studies. The restriction to studies published in English risked language bias. Steps were taken to minimise errors and bias during study selection and data extraction. Methodological study quality was assessed, but it was unclear how many reviewers completed this assessment.

The authors; decision not to combine the results statistically appeared justified, particularly given the heterogeneity in study designs of the included trials and the neuropathic conditions of the patients. Some information was provided about the direction of effect found with the intervention, but no data were provided on the magnitude of the effects observed with any of the interventions (particularly for pain outcomes). The authors acknowledged correctly that inclusion of uncontrolled studies meant that the results are vulnerable to various sources of bias.

The authors' cautious conclusions regarding the evidence from the uncontrolled studies in the review are likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was required in the treatment of refractory neuropathic pain, particularly head-to-head comparisons of treatments in clinical and real world scenarios. Consensus definitions of refractory neuropathic pain were needed.

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