Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain

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CRD summary
This review assessed the safety of long-acting formulations of tramadol hydrochloride in the treatment of chronic osteoarthritis pain and concluded that differences in formulations may influence rates of adverse events. However, these differences should be interpreted with caution. Potential bias in the review, heterogeneity among studies and their unclear quality, support the authors' recommendation to interpret the findings with caution.

Authors' objectives
To assess the safety of various long-acting formulations of tramadol hydrochloride in the treatment of chronic osteoarthritis pain.

Searching
MEDLINE and EMBASE were searched between 1997 and 2008 for publications in English. An updated search was performed in 2009. Search terms were reported.

Study selection
Clinical trials that assessed the safety of long-acting formulations of tramadol in 50 or more participants aged at least 18 years and with chronic osteoarthritis pain were eligible for inclusion. Eligible studies were required to report safety data with a comprehensive breakdown of adverse events.

The included trials were of patients aged up to 80 years. Most trials reported that patients had osteoarthritis of the spine, hip and/or knee; some patients had additional chronic painful conditions. The included trials assessed immediate release, sustained release, once a day and extended release tramadol formulations at 100mg/day to 400mg/day. Randomised controlled trials (RCTs) compared different formulations of tramadol to each other, placebo or diclofenac. Some trials had run-in periods. Some patients used concomitantacetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) as rescue medication for osteoarthritis pain. Trial duration ranged from five to 91 days in RCTs and between six and 12 months in long-term open-label trials. Most trials assessed change in pain intensity and function.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Rates for study discontinuation, discontinuation due to adverse events, overall adverse events incidence and the most common adverse events were extracted from individual trials.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Data were presented as a narrative synthesis presented by tramadol formulation.

Results of the review
Fifteen studies (n=6,142 patients) were included in the review: eight placebo-controlled double-blind clinical trials; five active-controlled double-blind clinical trials; and two long-term open-label trials with no comparator group.

The most common adverse events were gastrointestinal (nausea, constipation and vomiting) and central nervous system-related events (dizziness, somnolence and headache). Patients who received tramadol reported adverse event rates of 45% to 84% compared to 19% to 66% in patients who received a control; 80% to 90% of reported events were
described as mild to moderate severity. One open-label study reported rates between 88% and 91% in patients who received tramadol. Three fixed-dose and two flexible-dose studies showed contrasting findings for tramadol dose and rates of gastrointestinal and central nervous system-related events. Discontinuation rates ranged between 10.2% and 76%, of which between 1.7% and 53.7% were due to adverse events.

Incidence rates for different tramadol formulations overlapped for the most common gastrointestinal and central nervous system-related events. However, incidence of dizziness was higher for the long-acting formulations compared with tramadol immediate release and rates of gastrointestinal events were lower for some long-acting formulations compared to immediate release formulations (incidence rates were reported in the review). Three studies reported that incidence of adverse events was highest during initial treatment and declined with continued treatment. Similarly, five studies reported that discontinuation rates due to adverse events were highest during initial treatment compared to continued treatment.

Findings on treatment dose and adverse events were reported in the review.

**Authors’ conclusions**
Actions of different tramadol formulations were biologically similar, but differences in pharmacokinetics, drug-release patterns and availability may influence the incidence of adverse events associated with tramadol. Limitations of the qualitative analysis of heterogeneous studies suggest that the observed differences should be interpreted with caution.

**CRD commentary**
The review question was clearly stated. The literature search included two electronic databases and the search was restricted to published English-language articles, so potentially relevant studies may have been missed. The authors did not state how each stage of the review process was undertaken, so reviewer error and bias could not be ruled out. Most studies were double blind; the authors did not formally assess other criteria. The authors acknowledged some limitations with the included studies, such as methodological heterogeneity (treatment dose and duration and use of concomitant medication) and clinical heterogeneity. Therefore, a narrative synthesis was appropriate. The authors acknowledged that only one study reported treatment-related adverse events and it was not possible to determine the proportion of adverse events that were related to treatment in the remaining studies. They also acknowledged high discontinuation rates among studies that may have increased the potential for missing data.

Given the limitations with the review process and shortcomings of the included studies, the authors’ recommendation to interpret the findings with caution seems appropriate.

**Implications of the review for practice and research**
**Practice:** The authors stated that whether or not dose reductions were required during the first few weeks of treatment during continued therapy, patients were likely to tolerate treatment better once their optimal dose was identified. They stated that differences between tramadol formulations may help educate healthcare providers about tramadol treatment in patients with chronic osteoarthritis pain and help select optimal doses for individual patients.

**Research:** The authors did not state any implications for future research.

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Record Status
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