Ketamine in chronic pain management: an evidence-based review  
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CRD summary
This review assessed the effectiveness of ketamine for chronic pain. The authors concluded that there is moderate to weak evidence about ketamine and that further controlled trials are required. The lack of a validity assessment and the inadequate reporting of the methods used to conduct the review hamper an assessment of the evidence. The studies were generally of a poor quality, so the evidence is weak.

Authors’ objectives
To evaluate the potential effectiveness of ketamine for treating chronic pain.

Searching
MEDLINE and EMBASE were searched from 1966 to August 2002 without any language restrictions; the search terms were reported. In addition, the Reference lists of retrieved articles and reviews were checked. Abstracts and unpublished studies were excluded. Authors of studies were not contacted.

Study selection
Study designs of evaluations included in the review
Inclusion criteria relating to the study design were not specified. It seems that all study designs were eligible for inclusion in the review. The studies included were randomised controlled trials (RCTs), controlled trials, case series and case reports.

Specific interventions included in the review
Inclusion criteria relating to the interventions were not specified. However, it was clear that studies of ketamine were eligible for inclusion. In the included studies, ketamine was administered alone or in combination with other agents (including alfentanil, lidocaine, magnesium, morphine and placebo). Ketamine was given orally, intravenously, subcutaneously, or via an epidural.

Participants included in the review
Studies of people experiencing chronic pain were eligible for inclusion. The participants in included studies were people with: central pain, complex regional pain syndromes, fibromyalgia, ischaemic pain, non-specific pain of neuropathic origin, acute or chronic neuropathic pain, orofacial pain, phantom limb pain and postherpetic neuralgia.

Outcomes assessed in the review
Inclusion criteria relating to the outcomes were not specified. The outcomes reported included pain relief and adverse effects.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
Validity was not fully assessed. The authors did, however, grade the level of evidence from studies using a hierarchy of study design. Level I evidence came from systematic reviews of relevant RCTs; level II evidence from one or more well-designed RCTs; level III evidence from well-designed non-randomised controlled studies, well-designed cohort studies, or case-control studies; level IV evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative, grouped by type of pain.

How were differences between studies investigated?
Differences between the studies were not investigated or discussed. The authors stated that a meta-analysis was not appropriate because of variation in the study objectives and design, and the poor quality of the included studies.

Results of the review
Twenty-four studies (n=198) were included, of which seven were RCTs (n=114).

Central pain: one level II study (9 patients) and one level IV study (1 patient) found that oral and parenteral ketamine reduced continuous and evoked pain with modest side-effects.

Complex regional pain syndrome: two level IV studies (3 patients, 2 of whom also had concurrent physiotherapy and rehabilitation) found that epidural ketamine produced complete pain relief. One patient reported severe headaches and nausea.

Fibromyalgia: two level II studies (RCTs; 46 patients diagnosed using established criteria) found that ketamine increased endurance and reduced tenderness at trigger points (plus some other measures of pain) in comparison with lidocaine, naloxone and placebo.

Ischaemic pain: one level II crossover study (8 patients) found that intravenous ketamine (0.45 mg/kg) produced transient pain in all patients compared with 5 patients obtaining relief from morphine.

Orofacial pain: the results from level II and level IV studies were mixed. One level II crossover study (30 patients with trigeminal neuralgia) found little difference between ketamine and pethidine. One level IV study (7 patients) found ketamine relieved pain only in the 3 patients who had suffered pain for less than 3 years. One level II study (1 patient in n of 1 trial) found ketamine relieved pain in comparison with placebo.

Non-specific neuropathic pain: level II and level IV studies reported conflicting results. Three level II studies (24 patients with a variety of underlying conditions) found that ketamine reduced hyperalgesia and allodynia but there was less effect of continuous pain. One level IV study (1 patient) also found benefit from ketamine. One level II study (9 responders out of 21 initially entered patients) showed low response rates in n of 1 RCTs (2 of the 9 chose to continue ketamine). One level IV study (21 patients) found less favourable results and reported high drop-out rates due to side-effects and minimal benefit.

Phantom limb pain: one level II study (11 patients), one level III study (3 patients) and one level IV study (1 patient) found ketamine to be beneficial. The reviewers also reported positive results from another level IV study, but presented no details of this study.

Postherpetic neuralgia: one level II study (8 patients), one level II study (5 patients who were included in the level II study) and two level IV studies (2 patients) found that ketamine reduced pain. The level II study found that all patients reported side-effects with ketamine.

Acute on chronic episodes of severe neuropathic pain: one level IV study (1 patient unresponsive to morphine and intrathecal bupivacaine) found benefit from intravenous ketamine. The reviewers also reported results from their own experience of subcutaneous ketamine (classified as level IV evidence), but gave no supporting reference or details.

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Authors' conclusions
The evidence for the effectiveness of ketamine in treating chronic pain was moderate to weak, but it may be an option where standard analgesic treatments have failed. Further controlled studies are needed.

CRD commentary
Many details of the conduct of this review were unclear, such as the selection criteria for including studies and how these criteria were applied, and how the data were extracted (e.g. how many reviewers performed the data extraction). Therefore, it was not possible to judge whether bias could have occurred in the review process. The literature search was adequate and no language restrictions were applied. However, unpublished studies were not sought and conference abstracts were excluded, which might have led to some relevant studies being missed. The authors graded the level of evidence from the included studies according to study design, but did not undertake a detailed validity assessment. In addition, the authors referred to results from their own experience without providing any details or references. The narrative synthesis was appropriate given the variation in the included studies. A range of study designs were included but most were of poor methodological validity, such as case reports and case series, and the results of these were unlikely to be reliable. The authors’ conclusions may have overstated the potential effectiveness of ketamine, based on the results of this review.

Implications of the review for practice and research
Practice: The authors stated that a trial of ketamine is probably warranted for the patient with severe chronic pain that is incapacitating and refractory to other first- and second-line pharmacological therapies, but should only be regarded as a temporary measure.

Research: The authors stated that further controlled studies are needed.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.