Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications

Turner J A, Sears J M, Loeser J D

CRD summary
The authors concluded that in patients with a successful trial of the programmable intrathecal opioid delivery system (IDDS), noncancer pain appeared to improve with a permanent IDDS. However, long-term results were unclear and complications were common; further research is required. This was generally a well-conducted review and the authors’ cautious conclusion appears to reflect the limited evidence from observational studies.

Authors' objectives
To evaluate the effectiveness and complications of programmable intrathecal opioid/ziconotide delivery systems (IDDS) in patients with chronic noncancer pain.

Searching
PubMed (including MEDLINE), Science Citation Index Expanded, the Cochrane CENTRAL Register, EMBASE: Drugs and Pharmacology, Global Health, Current Contents Connect and International Pharmaceutical Abstracts were searched from inception to October 2005 using the reported search terms. In addition, reference lists of screened studies, the authors’ personal files, journals, books and reviews were screened and Medtronic Inc. were contacted for details of further studies. Journal articles published in English were eligible. Published conference abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Case reports were excluded. However, the review of complications also included reports of unusual serious adverse events. The duration of follow-up in the included studies ranged from 6 to 60 months; the duration of follow-up of individual patients varied considerably within most studies.

Specific interventions included in the review
Studies that evaluated opioid or ziconotide IDDS (or reported results separately for this intervention) were eligible for inclusion. Studies had to use opioid (with or without adjuvant medications) or ziconotide as the first intrathecal medication for all patients. Studies in which the type of pump was not clearly specified were excluded. No studies of ziconotide were identified. Where reported, in most patients in the included studies the initial IDDS drug was morphine; morphine was used either alone or in combination with other agents. The studies used a variety of doses and drugs over follow-up, with doses tending to increase over time. Systemic oral opioids were used concurrently in some studies.

Participants included in the review
Studies of patients with noncancer pain were eligible for inclusion. To be included in the review of effectiveness, studies had to report patient characteristics at baseline. Studies in which more than 10% of the patients were being treated for spasticity or pain associated with a specific disease (and which did not report the results separately for patients without this condition) were excluded, as were studies that only included patients who did not respond to the first IDDS drug (unless that drug was ziconotide). Some of the included studies only included patients with failed back surgery syndrome (FBSS); other studies included some patients with FBSS and some with other pain diagnoses. All of the primary studies included patients who had undergone a trial with an IDDS but did not have an IDDS implanted.

Outcomes assessed in the review
Studies that assessed pain, functioning or complications were eligible for inclusion. To be included in the review of effectiveness, studies had to report independent observer-completed or patient-completed standardised measures of pain or function assessed before and after the IDDS and at planned regular follow-up, and had to report pain and function outcomes for 75% or more of the patients at 6 or more months of follow-up. To be included in the review of complications, studies had to report complications 6 months or more after implantation for 80% or more of relevant
patients; studies that reported complications for only a subgroup of patients were excluded from this part of the review. In the review, complications were classified as biologic complications and hardware complications. The included studies assessed pain using 0-to-100 or 0-to-10 visual analogue scales (VAS) or a numerical rating scale for back pain.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies. Any disagreements were resolved by discussion.

Assessment of study quality
The authors did not state that they assessed validity. However, some aspects of validity were noted in the text. In addition, two reviewers independently graded studies using a hierarchy of study design (ranging from class I for randomised controlled trials to class VI for uncontrolled studies, case series, case reports and expert opinion) and some aspects of validity were noted in the text and tables. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by discussion. For each study in the effectiveness review, mean pain ratings were presented pre-IDDS and for the various reported follow-up periods.

Methods of synthesis
How were the studies combined?
Since the studies were clinically heterogeneous they were generally combined in narrative. In addition, mean pain intensity ratings (weighted by sample size) were calculated before and after IDDS implantation using data from studies that reported pain using VAS or numerical rating scales. Mean rates of specific complications (weighted by sample size) were calculated using data only from those studies that reported the specific complication.

How were differences between studies investigated?
Differences between the studies were discussed in the review or were apparent from the tables.

Results of the review
A total of 10 studies (n=342) were included in the review. Six observational studies were included in the review of effectiveness (258 patients with implanted IDDS).

In terms of quality, no randomised controlled trials (RCTs) were included in the review. All 6 studies included in the assessment of effectiveness were observational, and four had no comparison group.

All 6 studies of pain reported improved mean pain ratings in patients implanted with a permanent IDDS: the mean pain intensity score on a 0-to-100 scale was 82 pre-IDDS (3 studies) versus 45 at 6 months (3 studies) and 44 at 12 months (2 studies). Assuming patients lost to follow-up were failures, the proportions of patients reporting a 50% or more pain reduction were 30%, 38% and 56% at 6 months in 3 studies, and 44% after a mean follow-up of 29 months (1 study).

The authors stated that while all 6 studies reported some improvement in patient physical functioning with the IDDS, all the studies had major methodological flaws including the use of unvalidated measures, lack of reporting of relevant statistics, and high attrition rates.

There were 10 studies of complications. The percentages reported are weighted means. The most commonly reported drug-related adverse events were nausea/vomiting (33%; 3 studies), urinary retention (24%; 4 studies) and pruritus (26%; 3 studies). Non drug-related biologic complications included wound infection (12%; 3 studies), meningitis (2%; 3 studies) and pump malposition (17%; 2 studies). Hardware complications were common in the 2 studies that reported them and included catheter-related complications (18%; 2 studies), catheter migration/dislodgement (12%), catheter obstruction/occlusion (19%) and mechanical failure (5%). Surgery for revision of equipment was required in 27% (range: 13 to 39; 4 studies), and 5% of patients (range: 0 to 27; 7 studies) required permanent removal of the IDDS.

The review also reports less common serious adverse events.
Authors' conclusions
In patients with a successful trial of IDDS, noncancer pain appeared to improve after implantation of a permanent IDDS, but long-term results were unclear and drug-related and other complications were common. Further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and outcomes. The broad inclusion criteria for study design appear appropriate in view of the nature of the studies identified. Numerous potential sources were searched but no attempts were made to minimise either publication or language bias. Methods were used to minimise reviewer error and bias in the study selection and data extraction processes. Although there was no report of a formal assessment of validity, some aspects were discussed. Relevant information on the included studies was reported in the text and tables. In view of the clinical heterogeneity among the studies, the predominantly narrative synthesis was appropriate. This was generally a well-conducted review and the authors' cautious conclusion appears to reflect the limited evidence from observational studies. The recommendations for further research are supported.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that there is a need for adequately-powered, preferably RCTs comparing the IDDS with alternative treatments; in the absence of RCTs, prospective controlled trials with groups matched on relevant characteristics or large prospective cohort studies could be used. Outcomes should be evaluated using valid reliable measures, preferably for up to 2 years, and studies should be adequately reported (the authors listed factors that should be reported).

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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.