

Programmable Intrathecal Opioid Delivery Systems for Chronic Nonmalignant Pain: A  
Systematic Review of Effectiveness and Complications

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## **Executive Summary**

### Background and Objectives

This report summarizes the methods and findings of a systematic review of the literature on the effectiveness of programmable intrathecal drug delivery systems (IDDS) in reducing pain and improving functioning of individuals with chronic nonmalignant pain, as well as the literature on complications associated with IDDS. Two drugs have been approved by the United States (U.S.) Food and Drug Administration (FDA) for use in IDDS to treat pain: morphine and ziconotide (approved for use with patients who have an IDDS and have failed to respond to morphine); however, opioids other than morphine and adjuvant medications also are used commonly with IDDS for pain. We addressed two questions concerning intrathecal opioid and ziconotide delivery for the treatment of chronic nonmalignant pain via programmable IDDS:

1. What are the effects on pain and functioning, and do they change over time?
2. What are the types and rates of complications?

We also examined data on changes in IDDS drugs and doses over time and whether any articles that met our inclusion criteria for the review of IDDS effectiveness reported information on predictors of response to IDDS. Finally, we summarize the gaps in scientific knowledge of IDDS outcomes and complications, and make recommendations for future studies to better define the benefits and risks of this technology.

### Methods

Literature searches yielded 78 relevant articles. Six of these articles met the pre-specified inclusion criteria for the reviews of both IDDS effectiveness and IDDS complications, and four others met the criteria only for the review of complications. Two authors independently abstracted data from each article, then resolved discrepancies by discussion.

## Key Findings

- No studies of ziconotide met the inclusion criteria for either the effectiveness review or the complications review.
- Among the six studies that met the inclusion criteria for the IDDS effectiveness review, none was a randomized trial, two studies included comparison groups (but the comparison groups were methodologically problematic and there were no statistical comparisons), and the remaining studies were observational with measures of pain or functioning obtained before IDDS implantation and at follow-ups of varying lengths. All six included studies were Class IV, studies with the highest potential for bias.
- All six studies in the effectiveness review found improvement in pain on average among the patients who received a permanent IDDS and provided follow-up data. Across studies that provided patient visual analogue scale (VAS) or numerical rating scale (NRS) pain intensity ratings, the weighted mean = 82 pre-IDDS, 45 at 6 months, and 44 at 12 months (0 = no pain, 100 = worst pain). Three articles reported the “success rate” of IDDS in terms of the number of patients who continued to use their pump and had  $\geq 50\%$  reduction in pain at follow-up. These rates varied from 36% to 63% if patients lost to follow-up are not included and from 30% to 56% if patients lost to follow-up are considered failures.
- Patient pain intensity ratings appeared to remain fairly stable over the first year after IDDS implantation; data regarding whether the effects of IDDS on pain change after the first year are inconclusive. However, changes over time in drugs used with IDDS for individual patients and authors’ comments suggest that pain relief with morphine is not always adequate.

- All six articles in the effectiveness review reported some improvement in patient physical functioning with IDDS; however, serious methodological problems prevent conclusions regarding effects of IDDS on patient physical functioning or whether effects on function change over time. Only two studies used validated measures of function, both had serious methodologic flaws, and no studies were randomized trials. Only one article reported how many patients were receiving workers' compensation (11% of those trialed; percent of those with permanent IDDS was not reported). Only one article reported any outcomes information separately for workers' compensation patients; this article reported that of six workers' compensation patients, there was no significant change on a measure of functioning. However, statistical comparisons of workers' compensation and non-workers' compensation patients were not reported.
- We could not reach conclusions regarding the effects of IDDS on patient work status due to poor study methodological quality and reporting.
- The lack of randomized trials makes it impossible to evaluate the effectiveness of IDDS versus another treatment or "usual care" in improving pain and functioning in patients with chronic nonmalignant pain.
- The studies reviewed yielded little information on predictors of patient response to IDDS, although two studies raised the possibility that neuropathic pain may be less responsive than other types of pain to opioids delivered via IDDS.
- Complications with IDDS were reported commonly. These included drug side effects, other biological complications, and hardware-related complications.

- The most commonly reported drug side effects were nausea/vomiting (mean weighted rate across three studies reporting this complication = 33% of patients), urinary retention (24%, four studies), and pruritus (26%, three studies).
- Non-pharmacologic biological complications included wound infection (weighted mean across three studies = 12%), meningitis (weighted mean across three studies = 2%), and pump malposition (weighted mean across two studies = 17%).
- Catheter-related problems (e.g., migration, dislodgement, kinking, obstruction, occlusion) were reported commonly.
- More unusual serious adverse events reported with permanent IDDS have included intrathecal granulomas at the tip of the intrathecal catheter, some of which were large enough to cause spinal cord compression and neurologic dysfunction; traumatic syrinx; edema; postdural puncture headache; cranial nerve palsy; intracranial subdural hematoma; withdrawal symptoms; and opioid overdose.
- It is impossible to precisely estimate true rates of complications due to study reporting problems.
- We were unable to evaluate whether improvements in catheters over time have resulted in decreased catheter-related complications.
- Across the four studies that provided data enabling the calculation of equipment revision (reoperation) rates, 27% of patients (mean, weighted by study sample size; range, 13-39%) had one or more equipment revisions (mean of study mean follow-up lengths = 26 months).

- On average across the seven studies that reported this information, 5% (mean weighted by study size) of patients had their IDDS permanently removed by the time of follow-up (mean of study mean follow-up lengths = 32 months).
- Excluding one study that reported the trial dose as the “initial” intrathecal morphine-equivalent dose, the increase in mean intrathecal morphine-equivalent dose over time varied across studies from a 2.6-fold increase (from one month after implantation to a follow-up that ranged between 10 and 56 months) to a 7.4-fold increase (from the “initial” dose, with “initial” undefined, to a 24-month follow-up). The quality and quantity of reporting for dose escalation in these studies was not sufficient to allow more than these descriptive analyses.

### Conclusions

The six studies that met the inclusion criteria for the effectiveness review suggest that programmable intrathecal drug delivery systems improve pain among patients who report substantial pain relief with a trial IDDS and who can tolerate the pharmacologic side effects. However, definitive conclusions cannot be made concerning the effectiveness of IDDS relative to other treatments, sham controls, or “usual care” in improving pain, due to the lack of randomized trials. Although the studies reviewed reported some improvement in physical functioning, no definitive conclusion concerning the effects of IDDS on physical functioning can be reached due to the studies’ methodological problems. Only one study reported any physical functioning outcomes information separately for workers’ compensation patients, and this study reported that of six workers’ compensation patients, there was no significant change on a measure of functioning. Statistical comparisons of workers’ compensation and non-workers’ compensation patients were not reported. Many patients appeared to require increasing doses of

intrathecal morphine. Some patients could not tolerate morphine or did not have adequate pain relief with morphine and therefore received adjuvant medication with morphine or other medication. Use of these adjuvant medications is not approved in IDDS by the FDA, although such off-label usage is common and represents the standard of care. Complications involving pharmacologic side effects and hardware problems are common, as are reoperations. Other, more unusual but serious, adverse events were also reported (intrathecal granulomas at the tip of the intrathecal catheter, some of which were large enough to cause spinal cord compression and neurologic dysfunction; traumatic syrinx; edema; postdural puncture headache; cranial nerve palsy; intracranial subdural hematoma; withdrawal symptoms; and opioid overdose). Overall, the methodologic quality of the studies is quite poor.

#### Recommendations for Research

There is a need for large multi-center randomized trials comparing IDDS to other chronic pain treatment. In the absence of randomized trials, there is a need for large prospective cohort studies (ideally, with comparison groups of patients similar in demographic and pain characteristics but who do not receive an IDDS) in which standardized measures of pain, physical functioning, work status, and psychosocial functioning are administered independently of the treating team before the IDDS trial and at planned, regular follow-ups. Ideally, such studies would be coordinated so that the same measures are used, facilitating meta-analysis. Extensive efforts should be made to collect follow-up data on all patients enrolled, including those who do not go on to have permanent IDDS implantations and those who have permanent IDDS equipment removed. Finally, there is a need for systematic reporting across studies of whether or not each adverse event identified in this review occurred in the IDDS trial and with the permanent IDDS, and for events that occurred, the number of patients who had the event, the

number of patients assessed for the event, the severity of the event (for biological complications), the timing of the event relative to the IDDS implantation, and the duration of the event (for biological complications).

## **Abstract**

We conducted a systematic review of the literature on the effectiveness and complications of programmable intrathecal opioid and ziconotide drug delivery systems (IDDS) in relieving pain and improving functioning for patients with chronic nonmalignant pain. Literature searches yielded 78 pertinent articles. Six met the inclusion criteria for the effectiveness and complications reviews, and four others met the criteria only for the complications review; none were of ziconotide and none were randomized trials. Two authors independently abstracted data from each article, then resolved discrepancies by discussion. All six studies included in the effectiveness review found improvement in pain on average among patients who received a permanent IDDS and provided follow-up data (mean = 82 pre-IDDS, 44 at 12 months across studies that provided 0-100 pain scores). Rates of patients with  $\geq 50\%$  improvement in pain at follow-up ranged from 30-56% (three studies; patients lost to follow-up considered failures). All six articles also reported some improvement in physical function with IDDS; however, methodological problems preclude definitive conclusions. Only one study reported how many patients were receiving workers' compensation (11%). Only one article reported any outcomes information separately for workers' compensation patients, and this article reported that of six workers' compensation patients, there was no significant change on a measure of functioning. However, statistical comparisons of workers' compensation and non-workers' compensation patients were not reported. Patient pain intensity ratings appeared to remain fairly stable over the first year after IDDS implantation; data regarding changes after the first year are inconclusive. Intrathecal morphine-equivalent doses increased over time in each study that provided this information. Inadequate pain relief or side effects with morphine resulted in drug changes for some patients. The most commonly reported drug side effects with

permanent IDDS were nausea/vomiting (mean weighted rate = 33%, 3 studies), urinary retention (24%, 4 studies), and pruritus (26%, 3 studies). Catheter problems after permanent IDDS implantation were also reported commonly. Other more unusual, but serious, adverse events (e.g., granulomas at catheter tip) were also reported. We make suggestions for methodological improvements in future studies.

*Keywords:* Systematic review; intrathecal drug delivery systems; intrathecal opioids; chronic pain; failed back surgery syndrome

## 1. Introduction

Intrathecal opioid therapy via implantable drug delivery systems (IDDS) has been an option for the treatment of chronic pain since the early 1980s. The potential advantages of IDDS over other modes of opioid delivery include lower drug doses required for pain relief and hence less severe side effects. The first IDDS pumps delivered medication at a continuous rate. In 1988, a programmable IDDS pump [the Medtronic, Inc. (Minneapolis, MN) SynchroMed<sup>®</sup> pump] became commercially available and it has been used much more commonly than continuous infusion pumps over the past decade. The SynchroMed<sup>®</sup> pump remains the only commercially available programmable IDDS pump. This system consists of a pump implanted into an abdominal subcutaneous pocket; a catheter that is inserted into the intrathecal space of the spine and tunneled under the skin, connecting to the pump; and an external programmer that controls infusion rate and records medication concentration, volume, and dosage. The pump requires refilling regularly via subcutaneous port injections. Various screening trial techniques are used to select patients (usually on the basis of  $\geq 50\%$  pain relief and ability to tolerate the drug during the trial) for permanent implantation of the pump. Until recently, preservative-free morphine sulfate was the only drug approved by the United States (U.S.) Food and Drug Administration (FDA) for use in intrathecal pumps for pain treatment. In 2004, the FDA approved the use of ziconotide, a calcium channel blocker, in intrathecal pumps for patients with chronic refractory pain unresponsive to intrathecally-delivered morphine. However, off-label use of drugs in intrathecal pumps is common (Hassenbusch and Portenoy, 2000).

Given the high costs of chronic nonmalignant pain (Berger et al., 2004; Ekman et al., 2005; Maetzel and Li, 2002) as well as of IDDS (Hassenbusch et al., 1997; Kumar et al., 2002), there is an urgent need for high-quality data regarding the effectiveness of IDDS in relieving

pain and improving function. Conclusive information would be of great interest to patients with chronic pain, clinicians, and payers. Reviews of IDDS have been published (Bennett et al., 2000; Prager, 2002; Williams et al., 2000), but these are now several years old and they did not focus exclusively on studies of programmable IDDS for patients with failed back surgery syndrome (FBSS) and other nonmalignant pain syndromes that are not due to a specific disease. The authors of one of these reviews acknowledged as a limitation its inclusion of many different pump types and drugs in many different types of patients and pain problems (Williams et al., 2000).

We therefore conducted a systematic review of the literature through September 2005 focused on the effectiveness and complications of programmable IDDS with opioid medication or ziconotide for the treatment of chronic nonmalignant pain. We followed published guidelines for systematic reviews in the field of spinal disorders (van Tulder et al., 2003). We addressed two primary questions:

1. What are the effects on pain and functioning, and do they change over time?
2. What are the types and rates of complications?

We also examined data on changes in IDDS drugs and doses over time and whether any articles that met our inclusion criteria for the review of IDDS effectiveness reported information on predictors of response to IDDS. A final goal of this review was to summarize the gaps in scientific knowledge of IDDS outcomes and complications, and make recommendations for future studies that could better define the benefits and risks of this technology.

## **2. Methods**

### *2.1. Article selection*

With the help of an experienced health sciences librarian, we searched each of the following bibliographic databases from its starting date through October 10, 2005 (the starting date and number of articles identified from each database are specified in parentheses): PubMed including MEDLINE (1950; 460), Science Citation Index Expanded (1965; 346), Cochrane Central Register of Controlled Trials (1950; 32), EMBASE Drugs and Pharmacology (1980; 296), Current Contents Connect (1998; 167), Global Health (1973; 2), and International Pharmaceutical Abstracts (1970; 17). We tailored literature search strategies to the controlled vocabulary for each bibliographic database searched (see Appendix A). The search strategies did not include terms for health conditions or pain type due to the wide range of indications for IDDS and the broad diagnostic categories involved. Instead, we based the searches on four conceptual components: implantable, pump, intrathecal, and opioid (or ziconotide). We checked the search sensitivity by ensuring that almost all articles identified via manual bibliography reviews were identified via one or more of the structured bibliographic database searches. In addition, we asked a representative of Medtronic, Inc. for suggestions of articles to screen for inclusion. Finally, we searched our personal files, journals, and books, and reviewed the bibliographies of screened articles and previous systematic reviews for additional studies.

From these searches, we identified English-language articles relevant to IDDS effectiveness or complications among patients with chronic nonmalignant pain. Two authors (JAT, JMS) independently reviewed each of these articles to determine whether it met the following basic inclusion criteria for both the effectiveness and the complications reviews: (1) English-language journal article (published conference abstracts were excluded); (2) article addressed pain treatment with intrathecal opioid or ziconotide delivered via programmable pumps; (3) patient diagnoses not limited to spasticity or specific diseases (e.g., cancer, sickle cell

disease); and (4) article contained original data on pain, functioning, or complications in humans. Articles that did not meet these four criteria were not screened further.

Articles that did meet these basic criteria were reviewed independently by the same two investigators to determine whether they met the following more detailed inclusion criteria for both the effectiveness and complications reviews: (1) the only pump studied was programmable, or data were presented separately for patients with programmable pumps (if it was not clear what type of pump was received by all patients, attempts were made to contact the article authors for this information. In cases where the type of pump remained unknown, the article was excluded.); and (2) the first medication delivered intrathecally to all study participants was an opioid (with or without adjuvant medications) or ziconotide. The exclusion criteria for both the IDDS effectiveness and complications reviews were: (1) more than 10% of the sample were being treated for spasticity or pain associated with a specific disease [e.g., cancer, acquired immune deficiency syndrome (AIDS), sickle cell disease, multiple sclerosis, spinal cord injury] and data on pain, functioning, or complications were not presented separately for patients without these conditions; (2) study focused only on patients who did not respond to the first IDDS drug they were given (unless the study was of ziconotide); and (3) case report.

Two authors (JAT, JMS) independently used the American Academy of Neurology (AAN) Quality Standards Subcommittee classification scheme (Moxley et al., 2005) to classify the methodological strength of each study that met the inclusion criteria listed above. According to this scheme, Class I studies are randomized, controlled trials (RCTs) that meet additional specified methodologic quality criteria; Class II studies are prospective matched group cohort studies that meet specified methodologic quality criteria or RCTs in a representative population that lack one of the specified criteria for Class I RCTs; Class III studies are all other controlled

trials in a representative population with outcomes assessed independently of patient treatment; and Class IV studies are uncontrolled studies, case series, case reports, or expert opinion.

For the review of IDDS effectiveness, we applied three additional inclusion criteria: (1) Class I, II, or III study, or (due to the lack of Class I-III studies) a Class IV study with data from independent observer-completed or patient-completed standardized measures of pain or functioning obtained both before IDDS treatment (or ziconotide initiation) and at planned, regular follow-ups; (2) data from patient baseline descriptive and outcome measures reported for all study participants who underwent pump implantation (or ziconotide initiation) during the study period; and (3) original data reported on pain or functioning prior to IDDS treatment (or ziconotide initiation) and for  $\geq 75\%$  of implanted patients at  $\geq 6$  months follow-up.

Because some articles that did not meet the effectiveness review inclusion criteria did provide useful complications data, we used less restrictive inclusion criteria for the review of IDDS complications. For the complications review, we did not use the three inclusion criteria listed in the preceding paragraph. However, we required that the article report original data on complications for  $\geq 6$  months after pump implantation for  $\geq 80\%$  of patients who received a pump during the study period. We excluded articles that presented information only on a single complication of interest (i.e., we excluded articles that reported only on a subgroup of patients with a particular type of complication). Finally, articles that did not meet the criteria for the complications review were reviewed for reports of unusual complications that might not have been reported in the studies that met the inclusion criteria.

Two authors (JAT, JMS) used a structured form to screen each article for these inclusion and exclusion criteria. Discrepancies were resolved by discussion. The articles that met the

inclusion criteria for the effectiveness or complications review were examined closely to ensure that two or more articles did not report data from the same patients.

## *2.2. Review of included articles*

Two authors (JAT, JMS) independently read each article that met the inclusion criteria for the effectiveness or the complications review and recorded information using a structured abstraction form. Discrepancies were resolved by discussion. For both reviews, information was abstracted concerning study and sample characteristics, IDDS drugs and dosages initially and at follow-up assessments, and complications associated with the trial and with the permanent IDDS. For the effectiveness review, information was also abstracted concerning pain and functioning measures and results.

The complications portion of the abstraction form included a structured list of complications reported in articles we reviewed for the purpose of form development prior to screening articles as well as complications identified from one author's (JDL) extensive clinical experience. We grouped complications into two major categories: (1) biological complications, including infection, cerebrospinal fluid (CSF) leakage, pump rotation/malposition, and pharmacological side effects; and (2) hardware complications, including catheter-related problems, mechanical pump failure or battery failure within five years of implant, and programming or other technical problems. We also recorded data regarding operations to revise the equipment and to remove pumps permanently. In cases involving a complication that resulted from another complication, we recorded only the initial, causal complication; for example, if a catheter kink was described as resulting from pump rotation in the pocket, we recorded only the pump rotation as a complication. We abstracted all complications reported, including those that were not listed on the abstraction form.

### *2.3. Data analysis*

Because the studies reviewed were clinically heterogeneous, were not controlled or comparison trials, and used a variety of outcome measures, our analysis was generally qualitative rather than quantitative. However, we did calculate mean pain intensity ratings (weighted by study size) prior to and following IDDS implantation and the mean rate of each complication (weighted by study size) across those studies that provided sufficient data.

## **3. Results**

### *3.1. Search results*

Among all the articles identified through the search processes described above, after eliminating articles that did not meet the four basic inclusion criteria (e.g., languages other than English, review and other articles that did not involve patient samples, cancer pain, studies of non-programmable pumps), 78 appeared to be possibly appropriate for the systematic review. Two authors (JAT, JMS) independently reviewed each of the 78 articles using the structured checklist for the inclusion and exclusion criteria to make a final determination. Six articles met the inclusion criteria for the reviews of effectiveness and complications and four others met the inclusion criteria only for the review of complications. No studies of ziconotide met the inclusion criteria for either review. There were no RCTs of the effectiveness of programmable IDDS for chronic nonmalignant pain.

Fifty-two articles were excluded from both the effectiveness and complications review based on the same criterion. Of these, 26 were excluded because they were case reports (Aldrete et al., 1994; Bejjani et al., 1997; Belmans et al., 1997; Blount et al., 1996; Cabbell et al., 1998; Cherry and Eldredge, 1997; Dario et al., 1998; De Andres et al., 2000; Devulder et al., 1996; Fernandez et al., 2003; Groudine et al., 1995; Harney and Victor, 2004; Hu et al., 2002; Iacono et

al., 1994; Loughrey and Nedeljkovic, 2002; Macres and Richeimer, 2000; Mironer et al., 1998; North et al., 1991; Peng and Massicotte, 2004; Royal et al., 1998; Sauter et al., 1994; Shields et al., 2005; Staats et al., 2001; Toombs et al., 2005; Ubogu et al., 2003; Velarde et al., 2000), 13 because they did not exclusively involve programmable IDDS or did not present data separately for patients who received programmable IDDS (Bloomfield et al., 1995; Gay, 2002; Krames and Lanning, 1993; Leibrock et al., 2002; Penn and Paice, 1987; Raphael et al., 2002; Roberts et al., 2001; Schuchard et al., 1998a; Schuchard et al., 1998b; Thimineur et al., 2004; Valentino et al., 1998; Winkelmueller and Winkelmueller, 1996; Yoshida et al., 1996), nine because more than 10% of the sample had spasticity or a specific disease (see exclusion criteria in section 2.1) (Chambers and MacSullivan, 1994; Dario et al., 2005; Deer et al., 2002; Follett et al., 1992; Follett and Naumann, 2000; Hildebrand et al., 2001; Krames and Chapple, 2000; Levy, 1997; Taha et al., 2004), and four because the study focused only on patients who had not responded to the first IDDS drug they were given (Anderson et al., 2001; Mironer and Grumman, 1999; Mironer et al., 2002; Mironer and Tollison, 2001). Fourteen other articles were excluded from the effectiveness review because they did not meet the additional study methodology criteria for that review (Angel et al., 1998; Brown et al., 1999; Doleys et al., 1998a; Doleys et al., 1998b; Hassenbusch et al., 1995a; Hassenbusch et al., 1995b; Kamran and Wright, 2001; Kanoff, 1994; Njee et al., 2004; Paice et al., 1994; Raphael et al., 2004a; Raphael et al., 2004b; Tutak and Doleys, 1996; Willis and Doleys, 1999), and six because they did not report pre-IDDS data on pain or functioning (Abs et al., 2000; Aldrete and Couto da Silva, 2000; Finch et al., 2000; Jones et al., 2002; McMillan et al., 2003; Paice et al., 1996); the remaining six articles were included in the effectiveness review (Anderson and Burchiel, 1999; Anderson et al., 2003; Deer et al., 2004; Kumar et al., 2002; Kumar et al., 2001; Rainov et al., 2001). For the complications review, an

additional 16 articles were excluded because they did not report original data on complications for  $\geq 6$  months after pump implantation for  $\geq 80\%$  of study participants who received a pump during the study period (Abs et al., 2000; Aldrete and Couto da Silva, 2000; Brown et al., 1999; Doleys et al., 1998a; Doleys et al., 1998b; Finch et al., 2000; Hassenbusch et al., 1995a; Jones et al., 2002; Kamran and Wright, 2001; Kanoff, 1994; McMillan et al., 2003; Njee et al., 2004; Paice et al., 1994; Paice et al., 1996; Raphael et al., 2004a; Raphael et al., 2004b); this left ten articles that met the inclusion criteria for the complications review (Anderson and Burchiel, 1999; Anderson et al., 2003; Angel et al., 1998; Deer et al., 2004; Hassenbusch et al., 1995b; Kumar et al., 2002; Kumar et al., 2001; Rainov et al., 2001; Tutak and Doleys, 1996; Willis and Doleys, 1999). (Where there was more than one reason for exclusion, we noted only the first reason identified.)

The articles that met the inclusion criteria for either review were reviewed for redundancy. One investigator was an author on two articles (Tutak and Doleys, 1996; Willis and Doleys, 1999) included in the complications review, but the articles reported results from different studies (of different patients, using different IDDS trial procedures). Two investigators were authors on two articles included in the effectiveness and complications reviews (Anderson and Burchiel, 1999; Anderson et al., 2003), but the studies were of different patients enrolled during different time periods. Two patients may have been enrolled in two studies included in both the effectiveness and complications reviews (Anderson et al., 2003; Deer et al., 2004) (Valerie Anderson, personal communication), but the other patients differed in these studies and the articles reported different outcome measures. Finally, another two articles (Kumar et al., 2002; Kumar et al., 2001) that were included in both the effectiveness and the complications

reviews had the same first author, but reported on independent patient samples (Krishna Kumar, personal communication).

### *3.2. Study characteristics*

Table 1 summarizes features of the six studies that met the inclusion criteria for the effectiveness and complications reviews and the four additional studies that met the criteria only for the complications review. Among the ten articles, five did not report dates of study participant enrollment or pump implantation; in the other five, the beginning date ranged from July 1989 to February 1999 and the end date ranged from September 1992 to August 2000. The number of patients who received permanent IDDS ranged from 11 - 136 (total N = 342) and follow-up time ranged from 6 – 60 months across the ten studies. Four articles acknowledged funding from Medtronic, Inc., none acknowledged government funding, and six did not mention the source of financial support.

All six articles in the effectiveness review were observational. Four (Anderson and Burchiel, 1999; Anderson et al., 2003; Kumar et al., 2001; Rainov et al., 2001) were case series or cohort studies without comparison groups. [One of these studies (Anderson et al., 2003) involved a randomized comparison of the IDDS trial procedures, but not of the permanent IDDS.] In one study (Deer et al., 2004), data were collected prospectively from different centers and some follow-up information was provided for 14 of 30 (47%) patients who underwent a trial for IDDS but did not receive a permanent implant. However, the article did not include statistical comparisons of patients who did versus did not receive permanent IDDS. In the sixth study (Kumar et al., 2002), 88 patients who had failed to achieve satisfactory pain relief with spinal cord stimulation and thus had their stimulators removed were described as having been “randomly divided into two groups of 44 patients each and were matched for patient age and sex

and the number of [spine] operations undergone... Each patient was followed for a period of five years.” (page 804). Patients in one group received a trial of IDDS; the other group was not offered IDDS and continued to receive “conventional pain therapy.” Results were reported for patients in the first group who had a successful trial and subsequent permanent IDDS (those who failed the IDDS trial were not followed) and for patients in the second group; however, the two groups were not compared statistically at baseline or at follow-up.

Among the six studies in the effectiveness review, two were exclusively of patients with failed back surgery syndrome (FBSS) and the other four each included a number of patients with FBSS along with patients with other pain diagnoses. The mean percent of patients trialed who were implanted with a permanent pump was 72% (range, 52% - 87%) across the six studies. Only one article reported how many of patients studied were receiving workers’ compensation: 11.4% of those trialed (Deer et al., 2004) This article reported that medical insurance was not significantly associated with trial success.

### *3.3. Drugs and dosages*

Table 2 shows information relating to the intrathecal drugs and dosages used in each study initially and at the last follow-up. Seven articles provided information on morphine-equivalent doses “initially” and at follow-up; of these, all reported increases in morphine-equivalent doses over time. However, the definition of “initial” was not given in four of these studies, in one it was the dose during the trial, in one it was the dose at one month after the trial, and in one it was the dose three months after the trial. Excluding the one study that used the trial dose as the “initial” dose for reporting purposes, the increase in mean dose over time varied across studies from a 2.6-fold increase (from one month after implantation to a follow-up ranging 10 to 56 months) to a 7.4-fold increase (from the “initial” dose, with “initial” undefined,

to a 24-month follow-up). The quality and quantity of reporting for dose escalation in these studies was not sufficient to allow more than these descriptive analyses. Follow-up doses varied considerably within studies, and in small studies such as these, mean doses can be biased by outlying cases. Because of this, and because of the variable length of time from initial dose to “follow-up” dose within and across studies, it is not possible to calculate average dose increase per unit time. Furthermore, the time course of increases varied across studies. One article (Anderson and Burchiel, 1999) reported that the average intrathecal morphine-equivalent dose increased relatively rapidly during the first three to six months of IDDS therapy, then remained fairly constant over the next 12 months, then increased again from 18 to 24 months. Another article (Tutak and Doleys, 1996) reported that the average daily dose of intrathecal morphine increased gradually over the first 15 months, followed by smaller increases from 15 to 21 months. Yet another article (Rainov et al., 2001) reported stable mean morphine doses from one to three months, then gradually increasing morphine doses from 3 to 24 months.

In most studies, some patients required either adjuvant drugs added to morphine or change from morphine to another drug. This was to manage either inadequate pain relief or intolerable side effects. One article (Kumar et al., 2002) reported that because pain relief with morphine decreased despite dose escalation, four of 23 (17%) patients were changed to other drugs by six months after IDDS implantation. Another article (Anderson and Burchiel, 1999) reported that of 23 patients followed at 24 months, two (9%) had been switched to hydromorphone because of poor pain control with morphine, two (9%) had been switched to hydromorphone due to side effects of morphine, and five (22%) were on an opioid plus bupivacaine (see Table 2).

The literature also indicates that some patients with IDDS also use systemic (e.g., oral) opioid medication (Table 2). One article (Deer et al., 2004) reported that such supplementation increased over time. Relative to baseline, at 6 months, 65% of the patients had decreased or discontinued systemic opioids, but at 12 months, only 42.5% had.

#### *3.4. Effects on pain*

All six studies in the effectiveness review found improvement in pain with IDDS on average among the patients who received a permanent IDDS and provided follow-up data (Table 3). Weighted by sample size, mean pain intensity ratings on 0-100 scales across studies were 82 pre-IDDS (3 studies), 45 at 6 months (3 studies), and 44 at 12 months (2 studies). However, the attrition rate was high in the two articles that reported exact mean pain intensity ratings at a uniform follow-up time longer than 6 months and the pain intensity of patients lost to follow-up is unknown.

One article (Anderson and Burchiel, 1999) reported that patients' pain intensity ratings increased at 24 months (Table 3); however, changes in group averages are difficult to interpret due to study attrition. One other study (Kumar et al., 2001) also found that pain ratings increased at longer-term (after 18 months) follow-up. In both studies, average pain scores at the last follow-up were still substantially lower than pre-IDDS (Table 3). In another study, pain ratings remained fairly stable from 6 to 24 months (Rainov et al., 2001). Pain ratings were also stable from 6 to 12 months in a third study that did not include follow-up beyond 12 months (Deer et al., 2004).

Three articles reported the "success rate" of IDDS at follow-up in terms of the number of patients who continued to use their pump and had  $\geq 50\%$  reduction in pain. In the first of these (Anderson and Burchiel, 1999), eight of 22 patients (counting as treatment failures two patients

who discontinued therapy) who provided follow-up data at 24 months (out of 27 patients who received pumps and were still living at 24 months; three study participants had died of causes unrelated to the IDDS and five were lost to follow-up) had  $\geq 50\%$  decrease in pain. Thus, the success rate by this criterion was 36% not including patients lost to follow-up, and 30% if patients lost to follow-up were considered failures. In the second study (Kumar et al., 2001), six (38%) of the 16 patients implanted had  $\geq 50\%$  decrease in pain at 6 months and seven (44%) had this level of pain relief at the last follow-up (mean =  $29 \pm 12$  months). (This was the only article that provided information concerning change over time in proportion of patients who showed  $\geq 50\%$  pain relief.) In the third study (Anderson et al., 2003), 24 patients out of 27 implanted were assessed at 6 months and among these, 63% had  $\geq 50\%$  decrease in pain (the success rate is 56% if the three patients lost to follow-up are presumed to be treatment failures). The other three articles did not report success rates at follow-up.

One article (Deer et al., 2004) reported outcomes for 14 of 30 (47%) patients who underwent a trial for IDDS but did not receive a permanent implant (some had a successful trial, some did not). The authors reported that back and leg pain ratings “remained stable” in this group through six and 12 months after the baseline evaluation, in contrast to the decreases in the pain ratings of the IDDS group. However, the article did not report statistical comparisons of the two groups at baseline or at follow-up, adjusted for baseline differences.

### *3.5. Effects on functioning*

All six articles in the effectiveness review reported some improvement in patient physical functioning with IDDS; however, serious methodological problems prevent conclusions regarding effects of IDDS on patient physical functioning. Table 4 summarizes findings and methodological limitations of each study. In the study (Deer et al., 2004) that included outcome

information for 47% of the patients who underwent a trial for IDDS, the authors reported that Oswestry Disability Index (Fairbank and Pynsent, 2000) scores “remained stable” in this group through six and 12 months after the baseline evaluation, in contrast to improvements in the Oswestry scores of the IDDS group, but did not provide statistical comparisons.

Deer et al. (Deer et al., 2004) reported that among patients with baseline, 6-month, and 12-month Oswestry disability measure (Fairbank and Pynsent, 2000) scores, those not on workers’ compensation (n = 45) had statistically significant improvement from baseline to 12 months on the Oswestry, while patients (n = 6) on workers’ compensation did not change significantly (Table 4). However, the article did not report the results of a statistical analysis comparing Oswestry changes in the two groups after adjusting for other potentially important baseline differences between groups, the comparisons were of only the subset of patients with complete data, and the number of patients in the workers’ compensation group was very small, making it more difficult to show statistically significant change.

Four articles provided information on work status. The first (Anderson and Burchiel, 1999) reported that at baseline 47% of their sample (14 of 30 patients) was “disabled” and of the patients assessed at 24 months, 35% were disabled (7 of 20 patients). In the second study (Kumar et al., 2001), no patients were working at baseline and “there was no significant increase in number of patients returning to employment before and after intrathecal morphine therapy” (page 83). In the third study, two patients who had been working with intermittent time loss prior to implantation continued to work after implantation “with increased comfort and without any disruptions” and two patients unemployed before implantation were able to work part-time after implantation (Kumar et al., 2002). No patient in a comparison group of patients who received “conventional pain treatment” but not IDDS returned to work during the study period.

The fourth article (Deer et al., 2004) reported work status only for patients who provided baseline and 6-month data (105 of 136 patients implanted were assessed at 6 months). Among those working, working at reduced capacity because of pain, or not working because of pain at baseline (n = 69), 62% were at the same status, 25% were at a worse status, and 13% at a better status at 6 months. Among patients assessed at 12 months (n = 47), 68% were at the same status, 11% at a worse status, and 21% at a better status.

### *3.6. Do effects on pain and functioning change over time?*

We reviewed the articles that met the effectiveness review inclusion criteria for information concerning whether programmable IDDS effects on pain and functioning change over time. The data in Table 2 demonstrating increased morphine-equivalent doses over time and the fact that many patients were switched to drugs in addition to or instead of morphine after initially starting on morphine (as shown in Table 2) suggest that over time morphine has diminishing effects on pain and/or intolerable side effects for many patients. One article (Anderson and Burchiel, 1999) reported that the average intrathecal morphine-equivalent dose increased relatively rapidly during the first three to six months of IDDS therapy, remained fairly constant over the next 12 months, then increased again from 18 to 24 months, following the same time course as changes in patients' pain intensity ratings (which decreased at 3 months relative to baseline, remained stable from 3 to 18 months, then increased at 24 months in the patients assessed; see Table 3). However, attrition in this study makes interpretation of these changes problematic. One other study (Kumar et al., 2001) also found that pain ratings increased at longer term (after 18 months) follow-up; however, in both studies, average pain scores at the last follow-up were still substantially lower than pre-IDDS (Table 3). In another study, pain ratings remained fairly stable from 6 to 24 months (Rainov et al., 2001). Pain ratings were also stable

from 6 to 12 months in a third study that did not include follow-up beyond 12 months (Deer et al., 2004). In the only article that provided information concerning change over time in proportion of patients who showed  $\geq 50\%$  pain relief (Kumar et al., 2001), six (38%) of the 16 patients implanted had  $\geq 50\%$  decrease in pain at 6 months and seven (44%) had this level of pain relief at the last follow-up (mean =  $29 \pm 12$  months).

Little information bearing on changes in patient functioning over time was reported (Table 4). In one study (Anderson and Burchiel, 1999), mean scores on patient visual analogue scale ratings of functional limitations decreased from baseline to three months, then remained fairly stable through 24 months; however, the measure was unvalidated and the attrition rate was high. In this same study, total scores on the Chronic Illness Problem Inventory (Kames et al., 1984), a measure of various problems such as sleep, inactivity, and psychosocial functioning, were improved significantly at three to twelve months relative to baseline, but did not differ significantly from baseline at 18 and 24 months. As detailed in Table 4, serious methodological problems limited our ability to draw conclusions from the other studies concerning whether effects of IDDS on physical functioning changed over time.

### *3.7. Complications*

Of the 10 articles included in the complications review, eight did not provide any information concerning complications during the IDDS trial procedure. One article indicated only that there were no infections or meningitis (Kumar et al., 2001). Only one article provided complete data on trial-related complications (Anderson et al., 2003). These authors reported that pharmacologic complications during the trial were common. Most were mild, but 15 of 37 (41%) patients trialed had urinary retention and 10 of these required catheterization for several days. Nine of the 37 patients (24%) had trial procedure-related complications such as difficulty

accessing the intrathecal space, mild swelling and pain at the injection site, and postdural spinal headache.

Table 5 summarizes the types and rates of complications with permanent IDDS, as abstracted from articles that clearly reported the number of patients with a given complication and the number of patients assessed for that complication. If an article did not mention a specific complication, we did not include that article in the calculation of the mean rate across studies.

Non-pharmacologic biological complications included wound infection (mean weighted by sample size = 12% across 3 studies), meningitis (2%, 3 studies), and pump malposition (17%, 2 studies). CSF leaks during catheter placement leading to postdural headache were not commonly reported. Among the ten studies, seven (Anderson et al., 2003; Hassenbusch et al., 1995b; Kumar et al., 2002; Kumar et al., 2001; Rainov et al., 2001; Tutak and Doleys, 1996; Willis and Doleys, 1999) did not mention this complication at all, two (Anderson and Burchiel, 1999; Deer et al., 2004) mentioned it but did not provide both the number of patients assessed for this complication and the number who had the complication, and one (Angel et al., 1998) reported that no patients had it. In one study, one of 30 patients showed drug-seeking behavior and one patient received an overdose of morphine and bupivacaine due to a programming error (Anderson and Burchiel, 1999).

The most commonly reported drug side effects were nausea/vomiting (mean weighted by sample size = 33% of patients, 3 studies) (Angel et al., 1998; Tutak and Doleys, 1996; Willis and Doleys, 1999), urinary retention (24%, 4 studies) (Angel et al., 1998; Hassenbusch et al., 1995b; Tutak and Doleys, 1996; Willis and Doleys, 1999), and pruritus (26%, 3 studies) (Angel et al., 1998; Tutak and Doleys, 1996; Willis and Doleys, 1999). Other side effects mentioned in some articles in the complications review were provocation of asthma (Kumar et al., 2001), insomnia

(Kumar et al., 2001), dry mouth (Kumar et al., 2001), nightmares (Kumar et al., 2001), myoclonic jerk/spasm (Kumar et al., 2001), dizziness (Kumar et al., 2001; Willis and Doleys, 1999), loss of appetite (Kumar et al., 2001), diarrhea (Willis and Doleys, 1999), and headache (Willis and Doleys, 1999).

Hardware complications were reported commonly. Across the two studies that reported information sufficient to calculate the percent of patients who had one or more catheter-related complication after permanent IDDS implantation, the weighted mean rate was 18%. On average across studies (weighted by sample size), 12% of patients with permanent IDDS had catheter migration or dislodgement, 19% had a catheter obstruction or occlusion, and 5% had mechanical failure of the pump or battery (not including normal battery replacement). Across the four studies that provided data enabling the calculation of equipment revision (reoperation) rates, 27% of patients (mean, weighted by study sample size; range, 13-39%) had one or more equipment revisions (mean of study mean follow-up lengths = 26 months). On average across the seven studies that reported information on pump removal, 5% (mean weighted by study size; range, 0-27%) of patients had their IDDS permanently removed by the time of follow-up (mean follow-up = 32 months).

We were unable to evaluate whether improvements in catheters over time have resulted in lower rates of catheter-related complications such as kinking and breaking. As can be seen in Table 5, only two studies provided data that enabled the calculation of rates of one or more catheter-related complication, and they were published in the same time period (2001-2002). Only two studies reported data that enabled us to calculate rate of catheter migration or dislodgement; although the rate was higher in the 1995 than in the 2001 study, each study was quite small and it is unknown whether the lower rate in the 2001 study was due to a difference in

the catheters used. Only one other catheter complication (catheter obstruction/occlusion) rate could be calculated in more than one study and these studies enrolled all patients prior to 1996.

We reviewed articles that did not meet the criteria for the complications review for unusual adverse events that might not have been reported in the included studies (Table 6). There were a number of reports of intrathecal granulomas at the tip of the intrathecal catheter, some of which were large enough to cause spinal cord compression and neurologic dysfunction such as urinary incontinence and paraparesis or paraplegia (Aldrete et al., 1994; Blount et al., 1996; Cabbell et al., 1998; Fernandez et al., 2003; McMillan et al., 2003; North et al., 1991; Peng and Massicotte, 2004; Shields et al., 2005). There were case reports of traumatic syrinx due to penetration of the spinal cord by the intrathecal catheter (Harney and Victor, 2004); local erythema and edema in the area of the abdominal wall pocket and lower extremity edema (Mironer et al., 1998); transverse myelitis due to catheter-tip infection (Ubogu et al., 2003); postdural puncture headache, diplopia, cranial nerve palsy, and intracranial subdural hematoma (Velarde et al., 2000); and dissociative mental state (Loughrey and Nedeljkovic, 2002). There was a report of withdrawal symptoms due to catheter disconnection from the pump (Hu et al., 2002) and a report of a patient self-draining morphine from her pump to use parenterally (Cherry and Eldredge, 1997).

The articles that did not meet the inclusion criteria for the complications review but were reviewed for unusual adverse events contained several reports of opioid overdose from various causes: changes from one intrathecal opioid medication to another (Royal et al., 1998), programming errors (Belmans et al., 1997), surgeon flushing the line accidentally with morphine rather than saline after placing an intrathecal catheter (resulting in circulatory depression requiring inotropic support, dilated pupils, and seizures) (Groudine et al., 1995), and pump refill

via the side port instead of the drug reservoir port resulting in the morphine going directly into the CSF (Sauter et al., 1994). Groudine et al. (Groudine et al., 1995) also described two previous deaths reported to the device manufacturer resulting from massive intrathecal morphine overdoses due to mistakenly injecting morphine into an access port connecting directly to the cerebrospinal fluid.

### *3.8. Predictors of response to IDDS*

No study systematically examined predictors of response. One article (Kumar et al., 2001) reported that patients with nociceptive pain had the best pain relief initially after permanent IDDS implantation. In contrast, at an average of 29 months after implantation (when all patients were on morphine and two were also on clonidine), those with deafferentation pain had the best results, those with neuropathic pain had the least pain reduction, and those with mixed pain or nociceptive pain had a result in between. However, the size of each pain subgroup was very small and statistical analyses adjusting for other group differences that might have affected response were not reported. Another article (Deer et al., 2004) reported that there were no statistically significant associations between most factors assessed (patient age, patient gender, patient's previous pain treatments, whether psychological evaluations had been performed, clinical site, trial methods, trial duration, and medical insurance) and IDDS trial success. However, among patients who were trialed with opioids alone, patients with neuropathic pain had a significantly lower success rate than did patients with mechanical or mixed pain (89% versus 100%).

## **4. Discussion**

The strongest level of evidence for the efficacy of a pain treatment, at least one systematic review of multiple well-designed RCTs (McQuay et al., 1997), is not available for

programmable IDDS for chronic nonmalignant pain. The next strongest level of evidence (McQuay et al., 1997; van Tulder et al., 2003), a well-designed RCT of appropriate size, is also not available. Because there were no RCTs, we included in our review observational studies, including case series, that reported data from independent observer-completed or patient-completed standardized measures of pain or functioning before IDDS implantation and at planned, regular follow-ups. Case series are viewed as being the weakest study design for producing evidence on effectiveness of a treatment (Dalziel et al., 2005) because of selection and observer bias. In uncontrolled case series, it is not clear whether the outcomes are due to the intervention and to what extent positive outcomes reflect placebo effects. Furthermore, case series are subject to a variety of other biases, including sampling, detection, reporting, measurement, response, and publication (Dalziel et al., 2005). However, it may be necessary to review case series as part of health technology assessment when there is no stronger evidence and when the promise of the treatment or pressures surrounding funding make it unacceptable to await stronger studies (Dalziel et al., 2005). Significant changes in pain or functioning observed in such studies would support the need for methodologically stronger studies. Case series can provide credible adverse event information even if their effectiveness data are subject to uncontrolled bias.

All six studies that met the inclusion criteria for the effectiveness review used intrathecal opioids (sometimes with adjuvant medication); none used ziconotide. In each of these studies, pain improved on average among patients who received a permanent IDDS. Weighted mean pain intensity ratings on 0-100 scales across studies were 82 pre-IDDS, 45 at 6 months, and 44 at 12 months. However, the number of studies included in these averages was small and the attrition rate was high in the two studies that systematically reported exact pain intensity rating

scores at more than one follow-up; the average pain score at follow-up in these studies may be biased in unknown ways by the lack of inclusion of all patients who underwent IDDS implantation. Patient pain intensity ratings appeared to remain fairly stable over the first year after IDDS implantation; data regarding changes after the first year are inconclusive. However, changes over time in drugs used with IDDS for individual patients and authors' comments suggested that pain relief with morphine was not always adequate. In the articles that reported proportions of patients using IDDS with  $\geq 50\%$  pain relief at follow-up, these "success rates" (not including patients lost to follow-up) were 38% and 63% at six months, and 36% and 44% at follow-ups averaging two or more years.

Due to the absence of RCTs, no conclusions can be drawn concerning the effectiveness of IDDS relative to other treatments, sham controls, or "usual care". Also due to the lack of RCTs, we were unable to calculate the number needed to treat (NNT) (the number of people who would need to receive IDDS in order for one of them to obtain effective pain relief, as compared with no treatment, placebo, or another treatment) and the number needed to harm (NNH) (the number of patients who would need to receive IDDS in order for one of them to experience an adverse event) (McQuay and Moore, 1997).

The studies reviewed suggest that IDDS may improve patient physical functioning to some extent. However, no definitive conclusion can be reached concerning the effectiveness of IDDS in improving function or whether effects change over time because only two studies used validated measures of function, both had serious methodologic flaws, and no studies were randomized trials. We could not reach conclusions regarding the effects of programmable IDDS on patient work status due to poor study methodological quality and reporting.

Only one article (Deer et al., 2004) reported any outcomes information separately for workers' compensation patients; this article reported that of six workers' compensation patients, there was no significant change on a measure of functioning. However, statistical comparisons of workers' compensation and non-workers' compensation patients were not reported. A small retrospective study that did not meet the inclusion criteria for this review found that patients receiving versus not receiving workers' compensation did not differ in change in pain with IDDS, but those in the workers' compensation group reported somewhat less improvement in function (Doleys et al., 1998a). Two of 16 workers' compensation patients (12.5%) and 4 of 15 non-workers' compensation patients (26%) not working prior to implantation returned to work post-implant (the difference was not statistically significant).

The mean intrathecal morphine-equivalent dose change over time ranged from a 2.6- to 7.4-fold increase across studies that provided this information. Although these rates are affected by the length of time between the IDDS implantation and the "initial" dose reported as well as the length of follow-up, these data indicate that increasing opioid doses were needed to maintain pain relief. Furthermore, some patients required adjuvant medication with morphine or a different drug to manage inadequate pain relief or intolerable side effects with morphine.

The studies reviewed yielded little information on predictors of response to IDDS, although two studies raised the possibility that neuropathic pain may be less responsive than other types of pain to opioids delivered via IDDS. This is consistent with the impressions of many physicians who implant IDDS (Hassenbusch and Portenoy, 2000). Further research is needed to more rigorously evaluate whether certain types of pain respond differentially to different intrathecal drugs.

Although life-threatening complications with programmable IDDS pumps were rare, other adverse occurrences were reported frequently. These included drug side effects, other biological complications, and hardware-related complications. The most commonly reported non-pharmacologic biological complications were pump malposition (weighted mean = 17%) and wound infection (weighted mean = 12%). CSF leaks during catheter placement leading to postspinal headache have been reported to be common (Prager, 2002). We are uncertain as to why they were not more commonly reported in the studies we reviewed.

The most commonly reported drug side effects after permanent IDDS implantation were nausea/vomiting (weighted mean rate = 33% of patients), urinary retention (24%), and pruritus (26%). These rates are fairly similar to those reported in a previous review (Williams et al., 2000) that included different types of IDDS and drugs for both malignant and nonmalignant pain; those investigators found that the four most common drug side effects were nausea and vomiting (25%), sedation (17%), urinary retention (19%), pruritus (17%), and myoclonic activity (18%). However, we found only a 2% mean rate of sedation and little mention of myoclonic activity, although it was reported in one study (Kumar et al., 2001). Trial drug dosing as well as initial permanent IDDS drug and dose escalation will affect permanent IDDS drug side effects; evaluation of drug side effects reported with permanent IDDS must consider these parameters.

Intrathecal opioids have been reported to cause hypogonadism, amenorrhea, decreased libido, and erectile dysfunction, and it has been recommended that patients considering IDDS be informed of this (Abs et al., 2000; Finch et al., 2000; Paice et al., 1994). In our review, only two studies reported the percent of patients with sexual dysfunction (weighted mean rate = 25%). In future studies, sexual function should be assessed systematically.

Among the articles that did not meet the inclusion criteria for the complications review but were reviewed for unusual complications, there were a number of case reports of intrathecal granulomas at the tip of the intrathecal catheter that caused neurological injury. A review of the medical literature and of reports by Medtronic, Inc. to the U.S. FDA as of 11/30/2000 identified 41 cases of such granulomas from 1990 through 2000 (Coffey and Burchiel, 2002). The authors of that review concluded that some cases were undoubtedly missed and that it could not be determined whether the incidence of catheter tip mass lesions had changed during the 11-year interval covered by the report. The authors also concluded that the risk of a patient's developing a mass was not affected by age, sex, pain disorder diagnosis, or features of the IDDS. A more recent review also concluded that intrathecal catheter-related granulomas may be underreported in the literature (Miele et al., in press).

Catheter-related problems (e.g., migration, dislodgement, kinking, obstruction, occlusion) were reported commonly. We were unable to evaluate from the studies included in our review whether improvements in catheters over time have resulted in decreased catheter-related complications. On average across studies, 27% of patients (range, 13-39%) had equipment revision surgery and 5% (range, 0-27%) had their pumps removed permanently.

We caution that the mean complication rates we report may be quite different from actual rates. Several issues made it impossible to estimate true rates with any precision. First, if an article did not mention a complication, we had no way of knowing whether the complication occurred and was not reported or whether it did not occur. We did not include articles that did not mention a specific complication in the calculation of the mean rate for that complication across studies; this might have resulted in our reporting a mean complication rate higher or lower than the true complication rate. Second, it was often unclear how complications were assessed

(e.g., medical records review, systematic questioning of patients, patient spontaneous complaint). Obtaining information on complications through only one source may well result in underreporting of complications. Third, it was frequently unclear how many patients in a study had a particular complication and how many patients were assessed for that complication; thus, we could not calculate a rate for that study. Third, in some cases it was unclear whether a particular complication (e.g., a catheter problem) that occurred more than once in a study occurred only in different patients or occurred more than once in the same patient(s). A final issue for consideration is that symptoms presumed to be related to the intrathecal medication may in fact be due to other causes (e.g., diseases, non-IDDS medications); comparisons of rates of specific symptoms in groups of patients with IDDS with different drugs and in groups of patients taking different pain medications systemically but without IDDS are needed.

The rates and types of complications reported varied widely across studies, and it is probable that these differences are due to the small size of the studies as well as to differences in patients, IDDS hardware, clinical settings, surgeon experience with IDDS, complication assessment and reporting, length of follow-up (which varied widely within and across studies), and other factors. Large prospective studies with systematic assessment and reporting of all adverse events associated with trial and permanent pump implantation are needed in order to better estimate overall and specific rates of common as well as of more rare but serious adverse events.

The state of the literature on IDDS is fairly comparable to that of another chronic pain therapy requiring a surgical procedure, spinal cord stimulation (SCS). For both of these procedures, most studies are case series (Taylor et al., 2006; Turner et al., 2004). However, there is one important difference: there is one RCT of SCS (Kemler et al., 2000; Kemler et al., 2004).

Lumbar spinal fusions, yet another surgical procedure performed to relieve chronic low back pain, have been the subject of several RCTs involving comparisons to nonsurgical therapies (Brox et al., 2003; Fairbank et al., 2005; Fritzell et al., 2004). These RCTs of other surgical procedures could serve as examples to help guide the development of RCTs to evaluate IDDS.

Table 7 lists our recommendations for future studies to increase knowledge in these areas. Randomized trials are clearly needed. We acknowledge the difficulties of conducting a blinded comparison of IDDS with a placebo or sham control condition. Randomized comparisons of IDDS with other treatments (e.g., multidisciplinary rehabilitation treatment), although challenging due to the high costs of these treatments and need for large sample sizes, are possible and could be done in multi-site studies. RCTs of adequate size and design could yield important information concerning NNT and NNH. In the absence of randomized trials, there is a need for large prospective cohort studies in which standardized, validated measures of pain, physical functioning, work status, and psychosocial functioning are administered independently of the treating team before IDDS and at planned, regular follow-ups. Ideally, such studies would be coordinated so that the same measures are administered at the same intervals, facilitating meta-analysis. Extensive efforts should be made to collect follow-up data on all patients enrolled, including those who do not go on to have permanent IDDS and those who have permanent IDDS equipment removed.

We conclude that the literature on programmable IDDS for chronic nonmalignant pain suggests that programmable IDDS improves pain on average among patients who have a successful IDDS trial, although increases in opioid dosage and changes in medication are often needed to maintain pain relief. IDDS may improve patient functioning, but no definitive conclusion can be reached. Little can be learned from the literature regarding comparisons with

other treatments. Drug side effects and other complications requiring additional surgeries are common.

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Table 1

## Features of programmable IDDS studies included in effectiveness and complications reviews

Article	Study class *	Funding from IDDS manu- facturer?	N tried	N implanted	Sample	Study Dates	Follow-up, months (n)
<i>Effectiveness and complications reviews</i>							
Anderson & Burchiel (1999)	IV	Yes	40	30	Diverse diagnoses (14 FBSS); mean age, 58 yr.	NR	3 mo. (25), 6 mo. (25), 12 mo. (20), 18 mo. (20), 24 mo. (20)
Kumar, Kelly, & Pirlot (2001)	IV	NR	25	16	Diverse diagnoses (8 FBSS); mean age, 48 yr.	NR	6 mo. (16); variable after 6 mo.; mean, 29 mo.; range, 13-49 mo.
Rainov, Heidecke, & Burkert (2001)	IV	Yes	30	26	FBSS; median age, 54 yr.	NR	26 followed every 3 mo. for 24 mo., some followed longer; mean, 27 mo.; range, 24-42 mo.
Kumar, Hunter, & Demeria (2002)	IV	NR	44	23	FBSS; ages NR	NR	60 mo. (23)
Anderson, Burchiel, & Cooke (2003)	IV	Yes	37	27	Diverse diagnoses (28/37 trialed had FBSS); mean age, 55 yr.	6/97 – 8/00 (enrollment)	6 mo. (24)
Deer et al. (2004)	IV	NR	166	136	Back pain (66% of those trialed had FBSS); mean age, 56 yr.	2/99 – 2/00 (enrollment)	6 mo. (105), 12 mo. (72)
<i>Complications review only</i>							
Hassenbusch et al. (1995)	IV	NR	22	18	Diverse diagnoses; mean age, 50 yr.	7/89 – 9/92 (enrollment)	mean, 29 mo.; range, 10-56 mo.

Tutak & Doleys (1996)	IV	Yes	NR	26	Back, leg pain (22 FBSS); mean age, 44 yr.	NR	“average,” 23 mo.; range, 16-27 mo.
Angel et al. (1998)	IV	NR	13	11	9 FBSS, 2 neuropathic; mean age, 63 yr.	2/92 – 7/95 (referral)	mean, 27 mo.; range, 7-39 mo.
Willis & Doleys (1999)	IV	NR	NR	29	Back and/or extremity pain; mean age, 58 yr.	7/91 – 12/93 (implant)	mean, 31 mo.; range, 18-50 mo.

\* Studies were classified using the American Academy of Neurology Quality Standards Subcommittee classification scheme (Moxley et al., 2005) (see section 2.1).

FBSS = failed back surgery syndrome, IDDS = intrathecal drug delivery system, NR = not reported

Table 2  
 IDDS drug and dose initially and at last follow-up

Article	Initial IDDS drug(s) (n)	Initial intrathecal morphine-equivalent dose, mg/day, Mean (SD)	Final IDDS drugs (n)	Final intrathecal morphine-equivalent dose, mg/day, Mean (SD)
<i>Effectiveness and complications reviews</i>				
Anderson & Burchiel (1999)	Morphine (30/30)	1.96 (1.75) (“initial” not defined)	At 24 mo.: Morphine (14/23) Hydromorphone (4/23) (2 because of poor pain control with morphine and two because of morphine side effects) Bupivacaine with either morphine or hydromorphone (5/23)	At 24 mo.: 14.59 (20.5); 6/20 patients used oral opioids
Kumar, Kelly, & Pirilot (2001)	Morphine (16/16)	1.11 (1.91) (“initial” not defined)	At 29 mo. (mean; SD = 12 mo.): Morphine (12/14) Morphine with clonidine (2/14)	At 29 mo. (mean; SD = 12 mo.): 7.42 (4.20); 2 patients used oral opioids At 2 yr.: 5.2 (2.8)
Rainov, Heidecke, & Burkert (2001)	All 26 received morphine in combination with clonidine, bupivacaine, and/or midazolam	During trial: 0.5 (0.3)	At 2 yr.: Morphine (26) with bupivacaine (20), clonidine (16), and midazolam (10)	

Kumar, Hunter, & Demeria (2002)	Morphine (23/23)	NR	NR	At 6 mo.: Morphine (19) Clonidine (2) Hydromorphone (2)	NR
Anderson, Burchiel, & Cooke (2003)	Morphine (27/27)	0.87 (0.38) (“initial” not defined)	NR	NR	At 6 mo.: 4.1 (2.7); oral opioid dose decreased
Deer et al. (2004)	NR <sup>1</sup>	NR	NR	NR	At baseline, 88.2% of patients used systemic opioids. At 12 mo., relative to baseline, 11.9% had increased or started new systemic opioids, 45.8% had no change in systemic opioid use, and 42.5% had decreased or discontinued systemic opioids.
<i>Complications review only</i>					
Hassenbusch et al. (1995)	Morphine (8/18) Sufentanil (10/18)	At 1 mo.: 14.0 (1.9)	At 10-56 mo.: Morphine (7/18) Sufentanil (11/18)	At 10-56 mo.: 36.0 (6.7); 12/18 patients used oral opioids	At 10-56 mo.: 36.0 (6.7); 12/18 patients used oral opioids
Tutak & Doleys (1996)	Morphine (26/26)	At 3 mo.: 1.38; range, 0.48-6.09	At 16-27 mo.: Morphine (10/26) Morphine with tetracaine (14/26) Fentanyl (2/26)	At 21 mo.: 9.34 (range, 1.57-61.99); average oral morphine-equivalent dose = 175	At 21 mo.: 9.34 (range, 1.57-61.99); average oral morphine-equivalent dose = 175
Angel et al. (1998)	Morphine (11/11)	0.25-1.5 (“initial” not defined)	At 7-39 mo.: Morphine (11/11)	At 7-39 mo.: 1.5-14.0	At 7-39 mo.: 1.5-14.0

Willis & Doleys (1999)	Morphine (12/29) Hydro-morphine (16/29) NR (1/29)	Mean doses not reported	At 18-50 mo.: Morphine (1/29) Hydromorphone (13/29) Hydromorphone with lioresal (1/29) Fentanyl (8/29) Meperidine (4/29) Clonidine (1/29) One patient not followed	Mean doses not reported
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<sup>1</sup> Information not reported in article, but by personal communication, 56% morphine alone, 11% other opioid, 16% opioid and clonidine, 17% opioid and bupivacaine.

IDDs = intrathecal drug delivery system, NR = not reported

Table 3  
Mean pain ratings reported in the six studies reviewed for IDDS effectiveness

Study	Pain measure	Pre-IDDS pain (n)	3 mo. pain (n)	6 mo. pain (n)	12 mo. pain (n)	18 mo. pain (n)	24 mo. pain (n)	Other
Anderson & Burchiel (1999)	0-100 VAS average pain in past week	78.5 (30)	49.8 (25)	50.8 (25)	43.2 (20)	47.9 (20)	58.5 (20)	
Kumar, Kelly, & Piriot (2001)	0-100 VAS (timeframe unspecified)	91.8 (16)		24.3 (16)				34.2 (16) at last follow-up [mean (SD), 29 (12) mo.]
Rainov, Heidecke, & Burkert (2001)	0-10 VAS (timeframe unspecified)		Exact scores not reported; graph suggests approximately 8 on trial day 1, approximately 3 at 3 mo., approximately 4 at 6 mo., approximately 3 at 12 mo., and approximately 4 at 18 and 24 mo. (n = 26)					
Kumar, Hunter, & Demeria (2002)	VAS pain ratings obtained every 6 mo. in IDDS and comparison group, but scores in each group not reported							
Anderson, Burchiel, & Cooke (2003)	0-100 VAS average pain in past week		Mean scores not reported for the entire group of patients who received IDDS (scores reported only for subgroups), but approximately 81 pre-IDDS and 34-43 at 6 mo. (n = 24)					
Deer et al. (2004)	0-10 NRS back pain (timeframe unspecified)*	8.2 (134)		4.7 (105)	4.4 (72)			
<i>Mean **</i>		82.3		45.2	43.8			

IDDS = intrathecal drug delivery system; NRS = numerical rating scale; VAS = visual analogue scale

\* Scores shown are for back pain; article also reported leg pain scores.

\*\* Rainov et al. (2001), Kumar et al. (2002), and Anderson et al. (2003) not included; means calculated by multiplying mean pain score by number of subjects for each study, summing across studies, then dividing by total number of subjects across studies (converting the scores in the Deer et al. (2004) study to a 0-100 scale)

Table 4  
Effects of IDDS on physical functioning

Study	Reported effects of IDDS on physical function	Comments
Anderson & Burchiel (1999)	CIPi total scores improved somewhat during first 12 months, but did not differ significantly from baseline at 18 and 24 mo. CIPi sleep and social activities subscales, but not other subscales, were significantly improved relative to baseline at 24 mo. Mean patient ratings of functional limitations (0-100; higher scores = worse) were 80 at baseline (n=30), 63 at 3 mo. (n=25), 68 at 6 mo. (n=25), 60 at 12 mo. (n=20), 71 at 18 mo. (n=20), and 66 at 24 mo. (each follow-up rating significantly lower than baseline).	The functional limitations rating was not a validated, standardized measure.
Kumar, Kelly, & Pirlot (2001)	“At last follow-up, 9 (of 16) patients increased daily activities” (p. 82)	No scores on measures of function reported
Rainov, Heidecke, & Burkert (2001)	Approximately 19 of 26 patients reported improvement in walking ability at 2 yrs.	No scores on measures of function reported
Kumar, Hunter, & Demeria (2002)	Improvement of 27% averaged over a 5-yr period on the Oswestry physical disability measure; improvement of 12% in comparison group of conventional pain therapy (not IDDS)	Actual scores in each group at each assessment not reported; statistical comparison of follow-up scores relative to baseline in the two groups not reported. Unknown whether Oswestry score changes over time differed significantly between the IDDS and comparison groups.
Anderson, Burchiel, & Cooke (2003)	Scores on a measure of function improved from baseline to 6 mo.	Unclear whether improvement was clinically or statistically significant

Deer et al. (2004)	<p>Oswestry scores decreased from 44.8 (n=132) at baseline to 32.1 (n=90) at 6 mo. and 31.0 (n=59) at 12 mo. At baseline, 30% scored in the minimal to moderate disability range, and 60% in the severe range. At 12 mo., 73% were in the minimal to moderate range and 22% were in the severe range. At 12 mo., 66% showed improvement of at least one level on the Oswestry. Among patients with baseline, 6 mo. and 12 mo. Oswestry measures, those not on workers' compensation (n=45) had statistically significant improvement from baseline to 12 mo. on the Oswestry, while patients on workers' compensation (n=6) did not change.</p>	High loss to follow-up; unknown how those not followed differed (at baseline or at follow-up) from those assessed at follow-up.
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CIPi = Chronic Illness Problem Inventory, IDDS = intrathecal drug delivery system

Table 5  
Complications reported after IDDS implantation

Complication	Article	n with complication/ n assessed	% of patients with complication	Follow-up mean (range), months
<i>Non-pharmacologic complications</i>				
Wound infection	Angel et al. (1998)	0/11	0	27 (7-39)
	Kumar et al. (2001)	1/16	6	29 (13-49)
	Kumar et al. (2002)	5/23	22	60
	<i>Total</i>	<i>6/50</i>	<i>12</i>	
Meningitis	Angel et al. (1998)	0/11	0	27 (7-39)
	Kumar et al. (2001)	0/16	0	29 (13-49)
	Kumar et al. (2002)	1/23	4	60
	<i>Total</i>	<i>1/50</i>	<i>2</i>	
CSF leak	Angel et al. (1998)	0/11	0	27 (7-39)
Pump malposition	Hassenbusch et al. (1995)	2/18	11	29 (10-56)
	Kumar et al. (2002)	5/23	22	60
	<i>Total</i>	<i>7/41</i>	<i>17</i>	
<i>Pharmacologic side effects</i>				
Nausea/vomiting	Tutak & Doleys (1996)	3/26	12	23 (16-27)

	Angel et al. (1998)	3/11	27	27 (7-39)
	Willis & Doleys (1999)	16/29	55	31 (18-50)
	<i>Total</i>	22/66	33	
Sedation/ somnolence/ lethargy	Hassenbusch et al. (1995)	0/18	0	29 (10-56)
	Tutak & Doleys (1996)	1/26	4	23 (16-27)
	Angel et al. (1998)	0/11	0	27 (7-39)
	<i>Total</i>	1/55	2	
Urinary retention	Hassenbusch et al. (1995)	4/18	22	29 (10-56)
	Tutak & Doleys (1996)	2/26	8	23 (16-27)
	Angel et al. (1998)	2/11	18	27 (7-39)
	Willis et al. (1999)	12/29	44	31 (18-50)
	<i>Total</i>	20/84	24	
Pruritus	Tutak & Doleys (1996)	4/26	15	23 (16-27)
	Angel et al. (1998)	2/11	18	27 (7-39)
	Willis & Doleys (1999)	11/29	38	31 (18-50)
	<i>Total</i>	17/66	26	
Respiratory depression	Hassenbusch et al. (1995)	0/18	0	29 (10-56)
	Angel et al. (1998)	0/11	0	27 (7-39)
	<i>Total</i>	0/29	0	
Sexual dysfunction	Tutak & Doleys (1996)	1/26	4	23 (16-27)

	Willis & Doleys (1999)	13/29	49	31 (18-50)
	<i>Total</i>	<i>14/55</i>	<i>25</i>	
Constipation	Angel et al. (1998)	0/11	0	27 (7-39)
	Willis & Doleys (1999)	15/29	52	31 (18-50)
	<i>Total</i>	<i>15/40</i>	<i>38</i>	
Edema	Hassenbusch et al. (1995)	3/18	17	29 (10-56)
Diaphoresis	Tutak & Doleys (1996)	1/26	4	23 (16-27)
Urinary incontinence	Willis & Doleys (1999)	13/29	49	31 (18-50)
Hyperalgesia or allodynia	Anderson & Burchiel (1999)	0/30	0	24
Cognitive/mental status change	Hassenbusch et al. (1995)	0/18	0	29 (10-56)
<i>Hardware complications</i>				
One or more catheter-related complication	Kumar et al. (2001)	1/16	6	29 (13-49)
	Kumar et al. (2002)	6/23	26	60
	<i>Total</i>	<i>7/39</i>	<i>18</i>	
Catheter migration/dislodgement	Hassenbusch et al. (1995)	3/18	17	29 (10-56)
	Kumar et al. (2001)	1/16	6	29 (13-49)
	<i>Total</i>	<i>4/34</i>	<i>12</i>	

Catheter kinking <sup>1</sup>	Hassenbusch et al. (1995)	2/18	11	29 (10-56)
Catheter breakage <sup>1</sup>	Tutak & Doleys (1996)	1/26	4	23 (16-27)
Catheter obstruction/occlusion <sup>1</sup>	Tutak & Doleys (1996)	7/26	27	23 (16-27)
	Angel et al. (1998)	0/11	0	27 (7-39)
	<i>Total</i>	<i>7/37</i>	<i>19</i>	
Mechanical failure of pump or battery	Hassenbusch et al. (1995)	3/18	17	29 (10-56)
	Angel et al. (1998)	0/11	0	27 (7-39)
	Willis & Doleys (1999)	0/29	0	31 (18-50)
	Kumar et al. (2001)	1/16	6	29 (13-49)
	<i>Total</i>	<i>4/74</i>	<i>5</i>	
One or more equipment revisions (reoperation)	Hassenbusch et al. (1995)	7/18	39	29 (10-56)
	Tutak & Doleys (1996)	9/26	35	23 (16-27)
	Anderson & Burchiel (1999)	5/25	20	24
	Kumar et al. (2001)	2/16	13	29 (13-49)
	<i>Total</i>	<i>23/85</i>	<i>27</i>	
Pump removal (permanent)	Hassenbusch et al. (1995)	2/18	11	29 (10-56)
	Tutak & Doleys (1996)	1/26	4	23 (16-27)
	Angel et al. (1998)	3/11	27	27 (7-39)

Willis & Doleys (1999)	0/29	0	31 (18-50)
Kumar et al. (2001)	2/16	13	29 (13-49)
Rainov et al. (2001)	0/26	0	27 (24-42)
Kumar et al. (2002)	0/23	0	60
<i>Total</i>	<i>8/149</i>	<i>5</i>	

Note. Articles were included for each complication in this table only if they reported the number of patients with a particular complication and the number of patients assessed for that complication.

<sup>1</sup> One article (Willis and Doleys, 1999) reported that 3 of 29 patients (10%) had catheter kinking or obstruction, and 5/29 (17%) had catheter leakage or breakage.

CSF = cerebrospinal fluid

Table 6

## Reports of unusual adverse events

Adverse event	Study
Intrathecal granulomas at tip of intrathecal catheter	Aldrete et al. (1994), Blount et al. (1996), Cabbell et al. (1998), Fernandez et al. (2003), McMillan et al. (2003), North et al. (1991), Peng and Massicotte (2004), Shields et al. (2005)
Traumatic syrinx due to penetration of spinal cord by intrathecal catheter	Harney and Victor (2004)
Local erythema and edema in area of abdominal wall pocket	Mironer et al. (1998)
Lower extremity edema	Mironer et al. (1998)
Transverse myelitis due to catheter tip infection	Ubogu et al. (2003)
Postdural puncture headache, diplopia, cranial nerve palsy, intracranial subdural hematoma	Velarde et al. (2000)
Dissociative mental state	Loughrey and Nedeljkovic (2002)
Withdrawal symptoms due to catheter disconnection from pump	Hu et al. (2002)
Patient self-draining morphine from pump to use parenterally	Cherry and Eldredge (1997)
Opioid overdose	Royal et al. (1998), Belmans et al. (1997), Groudine et al. (1995)

Table 7

Recommendations for future studies and articles

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Study design

- Randomized trial comparing IDDS versus alternative treatment (e.g., multidisciplinary pain treatment) and/or “usual care;” if not possible, prospective nonrandomized comparison of IDDS to alternative treatment (if possible, with patient groups matched on important demographic and pain characteristics); if not possible, prospective cohort study
- Sample size based on a priori statistical power calculations

Assessment

- Timing: Before IDDS trial and at planned follow-ups at regular intervals up to at least one year and preferably two years (e.g., 6, 12, and 24 months)
- Measures: Valid, reliable patient self-report measures of pain, physical functioning, work status, and psychosocial functioning, with treating physician unaware of individual patient responses; assessment of complications using multiple sources of information (e.g., patient self-report, medical records review, treating physician-completed measures); if possible, ratings of patient functioning completed by someone other than patient
- Method: Patient-completed measures administered by someone not part of the treatment team; may be supplemented by objective measures (e.g., of physical functioning) completed by someone not part of the treatment team
- Follow-up assessment of all patients enrolled in study, regardless of IDDS status

Reporting

- Sample demographics, pain diagnoses, other relevant clinical characteristics
- Clinical and study-related inclusion and exclusion criteria

- Study enrollment dates
- Surgeon experience with IDDS (as this may affect outcomes and complications)
- Type(s) of pumps and catheters used
- Separately for patients who were trialed but who did not receive a pump and for those who did receive a pump, means and standard deviations of outcome measures prior to the trial and at six, twelve, and 24 months after the trial.
- Numbers of patients who (a) were approached for study participation, (b) were ineligible for the study, (c) were eligible but declined to participate, (d) underwent IDDS trial, (e) had a successful trial, (f) had an unsuccessful trial, (g) received permanent pump, and (e) provided data at each follow-up
- Statistical tests used (intent-to-treat analysis in RCTs) and results
- Among all patients enrolled, including those who did not receive a permanent implant, number and proportion with clinically meaningful improvement, as determined by criteria specified prior to beginning the study (e.g.,  $\geq 50\%$  pain relief), at 6 months, one year, and two years; and changes within patients over time in whether they meet the criterion for clinically meaningful improvement (e.g., among patients with  $\geq 50\%$  pain relief at 6 months, how many have this level of pain relief at one year?)
- Use of a standardized form for reporting the following information for each patient enrolled: (a) whether or not specific complications (including those identified in this review) occurred during the IDDS trial and during or following permanent IDDS implantation; (b) additional complications that occurred but were not on the standardized form; (c) for each complication that occurred, length of time between IDDS implantation and the complication, duration of the complication (if a biological complication such as a

drug side effect) and a rating of complication severity; (d) each battery change and length of time between implantation and the battery change.

- Source(s) of all funding for the study

## Appendix A: Literature Search Strategies

### PubMed

(synchromed[tw] OR (“injections, spinal”[mh] OR intrathecal[tw] OR subarachnoid[tw] OR subdural[tw] OR intraspinal[tw] OR spinal[tw]) AND (“infusion pumps, implantable”[mh] OR IDDS[tw] OR ((implanted[tw] OR implantable[tw] OR implantation[tw] OR chronic[tw] OR long-term[tw] OR intractable[tw] OR refractory[tw]) AND (“infusion pumps”[mh] OR “infusions, parenteral”[mh] OR infusion therapy[tw] OR infusion system[tw] OR infusion systems[tw] OR device[tw] OR devices[tw] OR drug administration system[tw] OR drug administration systems[tw] OR “drug delivery systems”[mh] OR drug delivery system[tw] OR drug delivery systems[tw] OR intrathecal infusion[tw] OR intrathecal administration[tw] OR intrathecal delivery[tw] OR pump[tw] OR pumps[tw] OR medtronic[tw]))) AND (“analgesics, opioid”[mh] OR “analgesics, opioid”[pa] OR “narcotics”[mh] OR “narcotics”[pa] OR narcotic[tw] OR narcotics[tw] OR opioid[tw] OR opioids[tw] OR opiate[tw] OR opiates[tw] OR “morphine”[mh] OR morphine[tw] OR “hydromorphone”[mh] OR hydromorphone[tw] OR dihydromorphinone[tw] OR dilaudid[tw] OR “oxymorphone”[mh] OR oxymorphone[tw] OR “methadone”[mh] OR methadone[tw] OR “heroin”[mh] OR diamorphine[tw] OR heroin[tw] OR “sufentanil”[mh] OR sufentanil[tw] OR sufenta[tw] OR “fentanyl”[mh] OR fentanyl[tw] OR “meperidine”[mh] OR meperidine[tw] OR demerol[tw] OR “ziconotide”[nm] OR ziconotide[tw] OR prialt[tw]) AND English[Lang]

### EMBASE Drugs and Pharmacology; Global Health; International Pharmaceutical Abstracts

(synchromed or ((Intrathecal Drug Administration/ or (intrathecal or subarachnoid or subdural or intraspinal or spinal).mp) AND (IDDS OR ((implant\$ OR chronic OR long-term OR intractable OR refractory) AND (infusion therapy OR infusion system\$ OR device\$ OR drug administration system\$ OR drug delivery system\$ OR intrathecal infusion OR intrathecal administration OR intrathecal delivery OR pump\$ OR medtronic).mp)))) and (narcotic analgesic agent/ or (narcotic\$ or opioid\$ or opiate\$ or morphine or hydromorphone or dihydromorphinone or dilaudid or oxymorphone or methadone or diamorphine or heroin or sufentanil or sufenta or fentanyl or meperidine or demerol or ziconotide or prialt).mp)

Limited to: human and English language

### Science Citation Index Expanded

(synchromed OR ((intrathecal OR subarachnoid OR subdural OR intraspinal OR spinal) AND (IDDS OR ((implant\* OR chronic OR long-term OR intractable OR refractory) AND (infusion therapy OR infusion system\* OR device\* OR drug administration system\* OR drug delivery system\* OR intrathecal infusion OR intrathecal administration OR intrathecal delivery OR pump\* OR medtronic)))) AND (narcotic\* OR opioid\* OR opiate\* OR morphine OR hydromorphone OR dihydromorphinone OR dilaudid OR oxymorphone OR methadone OR diamorphine OR heroin OR sufentanil OR sufenta OR fentanyl OR meperidine OR demerol OR ziconotide OR prialt)

Limited to: English and article

### **Cochrane Central Register of Controlled Trials**

(synchromed OR ((intrathecal OR subarachnoid OR subdural OR intraspinal OR spinal) AND (IDDS OR ((implant\* OR chronic OR long-term OR intractable OR refractory) AND ("infusion therapy" OR "infusion system" OR "infusion systems" OR device\* OR "drug administration system" OR "drug administration systems" OR "drug delivery system" OR "drug delivery systems" OR "intrathecal infusion" OR "intrathecal administration" OR "intrathecal delivery" OR pump OR medtronic)))))) AND (narcotic OR opioid OR opiate OR morphine OR hydromorphone OR dihydromorphinone OR dilaudid OR oxymorphone OR methadone OR diamorphine OR heroin OR sufentanil OR sufenta OR fentanyl OR meperidine OR demerol OR ziconotide OR prialt)

### **Current Contents Connect**

(synchromed OR ((intrathecal OR subarachnoid OR subdural OR intraspinal OR spinal) AND (IDDS OR ((implant\* OR chronic OR long-term OR intractable OR refractory) AND (infusion therapy OR infusion system\* OR device\* OR drug administration system\* OR drug delivery system\* OR intrathecal infusion OR intrathecal administration OR intrathecal delivery OR pump\* OR medtronic)))))) AND (narcotic\* OR opioid\* OR opiate\* OR morphine OR hydromorphone OR dihydromorphinone OR dilaudid OR oxymorphone OR methadone OR diamorphine OR heroin OR sufentanil OR sufenta OR fentanyl OR meperidine OR demerol OR ziconotide OR prialt)

Limited to: English and article