Health Technology Assessment

HTA Final Report Implantable Infusion Pumps for Chronic Noncancer Pain

Date: Friday, July 18, 2008

Presented By:

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Implanted Infusion Pumps for Chronic Noncancer Pain

Contract No. 6020-001788

Task Order No. 3

July 18, 2008

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Implanted Infusion Pumps for Chronic Noncancer Pain

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Executive Summary

This technology assessment was commissioned by the Washington State Health Technology Assessment Program for use by the Health Technological Clinical Committee (HTCC). The HTCC uses evidence, primarily as assessed in this report, to determine whether health technologies are safe, effective, and cost effective, and therefore should be covered by state programs that pay for health care. This systematic review evaluates relevant published research describing implantable infusion pumps in people with chronic non-cancer pain (CNCP). ECRI Institute's technology assessment provides an independent, in-depth, formal evaluation of the strength of evidence for the safety and efficacy of implantable infusion pumps for treatment of CNCP and its effects on overall health and quality of life.

The International Association for Study of Pain (IASP) defines chronic pain as pain lasting beyond the normal time of healing, defined as three months or longer.(1) CNCP can be due to any painful etiology other than cancer. It can result from any number of disorders, such as arthritis, postherpetic neuralgia, phantom limb pain, or pancreatitis. The most common source is low back pain, which can be the result of injury or disease.

CNCP is an important and common medical concern worldwide. A systematic review of four international studies conducted in developed countries found prevalence rates of any type and severity level of chronic pain in the general population to be as high as 55%. An estimated 9% of Americans and 19% of Europeans have moderate to severe CNCP. Risk factors for chronic pain include demographic and genetic factors. In general, older individuals and women are more likely to experience chronic pain. Individuals with a family history of CNCP may also be more likely to develop chronic pain, possibly due to central nervous system anomalies. Additional risk factors vary by the underlying cause of pain. The prevalence of chronic pain may increase in the United States (U.S.), as individuals are living longer, surviving pain-causing conditions, and developing risk factors for chronic pain (e.g., obesity, which can lead to or worsen conditions such as osteoarthritis and diabetic neuropathy) at increasing rates.

Chronic pain is burdensome and costly. Chronic pain causes not only unpleasant symptoms, it can also lead to decreased function, quality of life, and unemployment. Treating chronic pain can be costly, as multiple modalities may be utilized and frequent clinician supervision is required. There are many conservative treatments for CNCP, which clinicians select based upon the cause and severity of the patient's pain, and their co-morbidities and personal goals (e.g., activity level desired). Conservative treatments are often prescribed in combination and include but are not limited to: correction of the underlying disorder when possible, simple analgesics, antidepressants, anticonvulsants, opioids (usually administered orally or transdermally), physical therapy and massage, injections, acupuncture, and cognitive behavioral therapy. The goal of these treatments is to relieve pain, avoid substantial adverse effects, improve quality of life, and enable resumption of daily activities. When conservative treatments fail, surgery to correct the underlying cause of disease, if appropriate, may be considered.

Although conservative and surgical therapy provide adequate care for most CNCP patients, in some patients even exhaustive use of these methods fails due to insufficient pain relief or unacceptable adverse events. Failure of conservative therapy and inappropriateness for surgical therapy is the main indication for an implantable infusion pump. Additional criteria include definable cause of pain requiring constant treatment, passing a psychological evaluation, and undergoing a successful infusion trial that uses temporary means to simulate implantable infusion pump administration. Contraindications include surgical contraindications (e.g., infection, anticoagulation, inability to undergo general anesthesia), insufficient body size to support weight and bulk of the device, and life expectancy of less than three to six months. For intraspinal administration of opioids or ziconotide, patients should not have an occluded spinal canal, and for administration of any drug, no indication of spinal column instability.

Implantable pumps are devices which are fully surgically implanted into the patient to provide round-the-clock long-term drug therapy. In a surgical procedure, the pump itself is implanted, usually in the abdomen, and a catheter is tunneled to the site of drug delivery. Because medications are delivered

directly to the desired site, pain control is theoretically optimized while adverse events associated with systemic administration are theoretically minimized because the overall drug dose is reduced.

In this report we address the efficacy and effectiveness, harms, and cost issues associated with implantable infusion pumps. We systematically searched the peer-reviewed medical literature and other sources of information, and reviewed documentation provided to us by Washington State Health Technology Assessment Program. We searched for randomized controlled trials (RCTs) and other controlled trials, but none were identified that met our inclusion criteria. We identified 13 case series with 413 patients that evaluated the effectiveness and harms of implantable infusion pumps, three cost analyses that used data from 1,695 patients, and one cost analysis that used theoretical cost data.

Case series are generally considered a lower level of evidence for measuring the impact of an intervention than controlled trials in the treatment of CNCP. The reason is typically that, without a control group, there is no empirical estimate of what the patients' outcomes would have been if they had *not* received the treatment of interest. Thus, one would ideally have a control group in every circumstance. This is absolutely essential when patient's future outcomes are highly uncertain. However, if the natural history of a disease is stable, substantive improvement would not be expected without the intervention in question. Case series may therefore still provide meaningful information regarding a technology, especially when the natural history of the disease is well-known, and no substantial placebo effect is anticipated. This is especially true if a decision regarding the technology must be made and there is either no time to wait for controlled trial results to become available, or no controlled trials are expected.

Chronic noncancer pain patients who are candidates for receiving pain medication delivered by implantable infusion pumps have a fairly stable natural history of disease, lasting as long as a decade on average in some of the case series we identified. In addition, their course of disease would not be expected to vary as dramatically as other pain patients' because pump candidates have exhausted all other available interventions for pain, including surgery where appropriate, and have not had substantial reductions in pain. These individuals are therefore resistant to not only pain-reducing treatments, but also substantial placebo effects. We used case series in this analysis under the assumption that patients' future outcomes would be similar to their baseline outcomes.

In any systematic review, reviewers must decide how to summarize evidence from multiple studies. If case series satisfy our criteria and provide acceptable evidence, we do sometimes perform a meta-analysis using them. The meta-analysis of case series can follow logically from a) the consideration of case series based on sensitivity to patients' histories and possible futures and b) the aggregation of results using standardized meta-analytic techniques. Although there was variation across studies with respect to characteristics of enrolled patients and treatment protocols, all included studies addressed the use of implantable infusion pumps for CNCP. Therefore, provided all other criteria for meta-analysis were satisfied, we used meta-analysis to analyze the data for each outcome. Meta-analysis can reduce the risk of random error to produce a more reliable and precise effect estimate, and to potentially produce more generalizable results because the results from a variety of clinical contexts and settings are averaged. However, we did not necessarily use meta-analysis to arrive at a single point estimate for an effect size: In many cases we refrained from such an estimate. There are other reasons for utilizing meta-analytic techniques. These reasons apply regardless of whether the studies were all randomized and blinded studies, or a mix of blinded and unblinded studies, or a mix of randomized and non-randomized studies, or consisted solely of case series (as in this review).

- Increasing the power of an evidence base to determine the general direction of effect (i.e., an increase or decrease), especially when an evidence base is comprised of many small studies that, considered in isolation, could lead to a Type II error (concluding there is no effect when there really is one).

- Transparent methodology for drawing conclusions, or for deeming the findings too inconclusive or unstable to enable conclusions, thereby limiting the influence of subjective judgment on conclusion formation.
- Formal, objective methods to evaluate the consistency and robustness of conclusions.
- Provision of formal, objective framework that can be used to investigate potential reasons for different findings across studies. Using the meta-analytic techniques of meta-regression and subgroup meta-analysis, one can investigate whether differences in outcomes are potentially associated with differences in study protocols (e.g. drug administered, duration of treatment) or characteristics or patients enrolled (e.g. most common painful condition). This could potentially enable identification of study protocols associated with better or worse outcomes and patient groups who are most or least likely to benefit from therapy with an implantable infusion pump.
- Avoiding the pitfalls of narrative systematic reviews, such as vote count methods in which the qualitative findings of each study in the evidence base is considered side-by-side but never pooled quantitatively or considered with respect to the sample size (i.e., precision) of each study, possibly leading to erroneous results, and imprecision in assessing relationships between outcomes and potential moderator variables, especially as the number of studies increases.(2,3) Vote counting has been recommended as a method of "last resort," to be performed only when effect sizes and significance levels of the studies are unavailable.(3)

A potential risk of meta-analysis occurs when summary findings are used to draw conclusions without critically evaluating the evidence base. To prevent this risk, ECRI Institute uses a system of *a priori* systematic protocols to evaluate the evidence base for each outcome in a transparent and reproducible manner that only allows for conclusions to be drawn when the evidence base has satisfied specific criteria. Our protocols and the specific risks they are intended to minimize are summarized in Table 1, below, and are fully explained in Appendix B.

Table 1. The ECRI Institute System's Quality Control Measures for Drawing Conclusions

Threat to Validity of Conclusion	ECRI Institute Protocol	ECRI Institute Quality Control Measure
Unacceptably low internal validity (e.g., quality)	All studies meeting other inclusion criteria are evaluated using internal validity scales selected with respect to study design type	Exclude studies with unacceptably low quality scores from evidence base.
Too few studies	The number of studies reporting an outcome is considered before performing meta-analysis or attempting to draw a conclusion	If fewer than three studies address an outcome in a statistically compatible manner, no quantitative conclusion is drawn. If only two studies are identified and they are qualitatively consistent, a qualitative conclusion may be possible.
Lack of unresolved consistency among studies (i.e., substantial heterogeneity)	Evaluate evidence base (all studies being considered for a given meta-analysis) for consistency using meta-analytic statistics. When inconsistency is detected, attempt to resolve it using statistical techniques if possible.	Evidence bases with unresolved inconsistencies are considered quantitatively unstable. No quantitative conclusion is drawn from them.(See Decision Point 4) We may present the meta-analytic findings for the consideration of decision-makers, but we do not draw evidence-based conclusions regarding them. Qualitative conclusions may still be possible.
Lack of robustness in summary statistic	Evaluate evidence base for robustness using meta-analytic	When lack of robustness is detected, the strength of evidence for the qualitative conclusion is downgraded, or, no qualitative

Threat to Validity of Conclusion	ECRI Institute Protocol	ECRI Institute Quality Control Measure
	statistics.	conclusion is drawn at all, in which case the evidence base is considered inconclusive.

We examined this evidence base in the context of four clinical questions, which are listed below along with our findings. For clinical outcomes, our strength and stability of evidence ratings take into consideration the internal validity rating, quantity, consistency, and robustness of the evidence.

Effectiveness and Harms

That this data come from uncontrolled case series should be considered when interpreting this finding.

All of the 13 included case series assessed the use of implantable infusion pumps for intrathecal delivery of opioids. Almost all used programmable pumps. Enrolled patients had a variety of neuropathic and/or nociceptive painful conditions, most frequently failed back surgery syndrome (FBSS). Reported mean durations of chronic pain were most frequently at least six years and as long as ten. In the seven studies that reported baseline visual analogue scale (VAS) at baseline, the pooled average pain score was 8.7 (standard deviation [SD] 2.7) out of 10, with 10 being unbearable pain and 0 being no pain. Most of the studies reported mean ages in the mid-forties to mid-fifties and enrolled more women than men. All patient characteristics and treatment protocols appear in evidence tables in appendices of the main body of the report.

Detailed internal validity assessments were conducted by outcome, and the overall internal validity rating for each outcome for which assessment was conducted were within the low range. Factors potentially limiting internal validity varied by study but included high attrition, failure to compare characteristics of completers and non-completers, use of ancillary treatments, and funding from a source with a financial interest in the outcome.

The evidence was sufficient to permit conclusions for some outcomes, but not for others. When data were inconclusive or unstable, we provide specific reason(s) for the lack of conclusions.

Question 1. What is the evidence of efficacy and effectiveness of implantable infusion pumps?

Findings for these outcomes are described in the following text and summarized in Table 2, which follows the text.

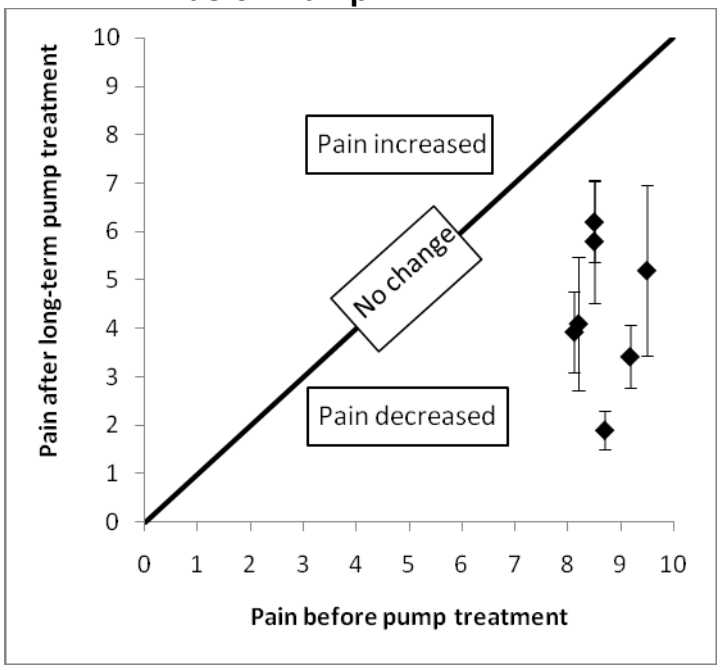
Pain and Pain Relief

Drug infusion with an implantable pump leads to clinically significant pain relief in patients with CNCP. (Strength of evidence: Weak).

In all seven studies (n = 146) included for this outcome, opioids were delivered to the intrathecal space by the implanted infusion pump. Six of those studies administered morphine with or without an adjuvant medication, and the seventh administered methadone. Most studies enrolled patients with failed back surgery syndrome (FBSS), one enrolled patients with neuropathic pain, one enrolled patients with various non-cancer causes of pain, and one enrolled patients with osteoporotic vertebral fractures. This evidence base was rated as low in internal validity.

Each study showed a mean reduction in pain from baseline to longest follow-up point (see Figure 1, below); these reductions in pain were statistically significant for all studies.

Figure 1. Average Pain Scores Before and After Treatment with Implantable Infusion Pump



Vertical error bars show 95% confidence intervals (CI)

Differences in study findings were detected when the studies were pooled. Overall, the pre-post change in visual analogue scale (VAS) scores on a scale of 0-10 showed a reduction in pain from 8.7 (SD 2.71) at baseline to 4.3 (SD 0.70) at longest follow-up. On average, the patients in these studies went from having severe pain at baseline to moderate pain at longest follow-up, depending on the method used to calculate long-term follow-up scores. We investigated several potential explanations for the differences among study results, but none were statistically reliable. However, this evidence base may have been too small to detect such associations. Because of the unexplained differences in the amount of average pain relief, we did not draw any quantitative conclusions regarding the average pain relief.

It is possible that some placebo effect may account for part of the pain relief reported. A Cochrane Review evaluated the influence of placebo interventions for clinical conditions including pain, found a possible placebo effect on reduction of patient-reported pain (although the authors note that it is unclear whether this effect size is clinically importance, and that it cannot be clearly distinguished from other potential sources of bias). The size of this effect was estimated at a SMD of only -0.25 (95% CI -0.35 to -0.16), which corresponds to a change in VAS of 6/100 (or 0.6/10).(4,5) This effect size is small compared to the pooled SMD of pre-post pain scores calculated in this report, suggesting that the reported pain relief after pump implantation was not solely due to a placebo effect.

Dichotomous Pain Scores

At least 25% Reduction in Pain Score

Six studies (n = 123 enrolled) reported the proportion of patients with at least a 25% reduction in pain (or sufficient data to enable us to calculate it). The primary cause of pain was failed back surgery syndrome in three studies, various causes in one study, osteoporotic vertebral fractures in one study, and neuropathy in one study. Drugs administered by pump to the intrathecal space were predominantly morphine, but in one study each there was an alternative of sufentanil citrate, clonidine if needed in addition to morphine, and methadone only.

The median internal validity score of these studies was within the low range. The proportion of patients who attained at least 25% pain relief varied considerably among the studies, from 37% to 100%. Statistical investigation of factors that may have influenced how many patients attained at least 25% pain relief were investigated. No factor associated with the outcome was identified, so the differences among studies remain unexplained. We pooled the findings from these studies and estimated that 56.3% (95% CI 33.7%-73.3%) of patients had at least a 25% reduction in pain. However, because of the unexplained differences among studies, we do not draw an evidence-based conclusion regarding the specific proportion of patients who reach this reduction level.

At least 50% Reduction in Pain Score

Seven studies (n = 150 enrolled) reported the proportion of patients who had at least a 50% reduction in pain scores (or sufficient data to enable us to calculate it). Patients were given morphine in six studies, an alternative of sufentanil in one of those studies, clonidine in addition to morphine if needed in one of the morphine studies, and methadone in the sixth study. Patients had chronic pain due to failed back surgery syndrome in four studies, osteoporotic vertebral fractures in one study, pain due to various causes in one study, and exclusively neuropathic pain in the remaining study.

The median internal validity score of this evidence base was within the low category. The percentage of patients who attained at least 50% pain relief varied widely among the studies, from 11% to 100%. We pooled the proportions of patients who attained at least 50% reduction in pain scores and found large variation among the studies. These differences could not be explained using statistical methods, although the small number of studies may be the reason why. Overall, an estimated 40.8% (95% CI 25.2%-58.5%) of CNCP patients had at least a 50% reduction in pain with intrathecal opioid use. However, because the proportion was inconsistent among studies, we consider the statistic unstable and do not draw an evidence-based conclusion from it.

Discontinuation from Clinical Study due to Insufficient Pain Relief

Of patients who began treatment with an implantable pump used for intrathecal opioid delivery for CNCP, 8.0% (95% CI 3.8%-15.8%) discontinued treatment in the clinical trial due to insufficient pain relief. (Stability of evidence: Low)

Five studies (n = 102) on intrathecally-administered opioids reported discontinuation from clinical study due to insufficient pain relief. All studies administered strong opioids—usually morphine, with clonidine if needed in one study, and sufentanil citrate as an alternative in another study. Most patients had pain due to failed back surgery syndrome, and in one study, each patient had neuropathic pain or pain due to various causes. These studies had a median internal validity score within the low range.

Only one or two patients per study (with 11-27 total patients enrolled per study) discontinued due to insufficient pain relief. The percentage of patients who discontinued from the clinical study ranged from 3% to 13%. When the studies were combined in a meta-analysis, the findings were consistent. An estimated 8.0% (95% CI 3.8%-15.8%) of patients discontinued their participation in the study due to insufficient pain relief. This estimate was robust to statistical tests, and we rated the stability of the estimate as low due to the low internal validity of the studies.

Quality of Life

It is not possible to determine whether long-term use of intrathecal opioids change the quality of life for patients with CNCP, because the two studies that met inclusion criteria for this outcome had inconsistent findings (one found improvement, but the other did not).

Two studies (n = 48) reported this outcome. In one study, infused methadone was studied in patients with failed back surgery syndrome who had lack of success with previous infused medications. In the other, infused morphine was studied in patients with osteoporotic vertebral fractures. The evidence base was rated as low internal validity overall. The two studies had qualitatively inconsistent findings. One did not observe a change in categorization of the quality-of-life scores after six months of treatment. The other found a dramatic improvement in quality of life after one year of treatment. We therefore found the evidence to be inconclusive. It is unclear why the findings of these studies differ; there are too few studies to investigate these differences statistically. Possible explanations include differences in patient population and treatment protocols, as well as the instrument used to measure quality of life.

Functional Status

Because only one study reported this outcome, there was an insufficient quantity of evidence to permit a conclusion for this outcome.

One study of low quality met inclusion criteria for this outcome. This study assessed functional status in patients who predominantly had failed back surgery syndrome and were treated with intrathecal morphine. Although this study reported a statistically significant mean improvement in function, data from one low-quality study provides insufficient evidence to form evidence-based conclusions. Therefore, no conclusions can be drawn for this outcome.

Change in Employment Status

Current evidence is insufficient to determine whether implantable infusion pumps are associated with a change in employment status among patients with chronic noncancer pain.

Our searches identified four studies that enrolled 115 patients and compared the proportion of 83 patients working or otherwise appropriately occupied (e.g., homemaker, student, retired for reasons other than pain) before and after implantation. Not all enrolled patients were considered for this outcome because in one study, only patients considered eligible for employment were considered. These studies enrolled patients with CNCP due to various or unspecified causes, or various conditions with failed back surgery syndrome being the most frequent cause. All of the studies administered morphine. Two offered an alternative of fentanyl, and one of those studies also offered alternatives of hydromorphone or methadone. Overall, the evidence base was rated as low in internal validity.

All four studies reported improvements in employment rates. However, not all studies reported statistically significant improvements in employment rates. The odds ratio of improved rate of employment after pump implantation compared to working before implantation is between the 95% CI 0.941 and 4.767. This interval is large enough to include two incompatible possibilities: that employment

reduces slightly after pump implantation (i.e., an odds ratio less than 1), and that employment increases greatly after pump implantation (i.e., an odds ratio greater than 4). Thus, current evidence is too imprecise to permit a conclusion about this outcome.

Use of Other Medications and Treatments

Intrathecal administration of opioids by implantable pump was associated with an overall decrease in the quantity of other drugs taken or a decrease in the proportion of patients taking other drugs.

Nine studies reported use of other medications in a total of 347 implantable pump recipients. Due to differences in reporting among studies, these studies cannot be combined in a meta-analysis to estimate the size of this effect. We did not rate the strength or stability of this conclusion because of the unclear relationship between use of additional medications and clinical outcome, due to the confounding influence of factors such as study protocols and use of medications for indications other than chronic pain.

Despite the differences in ways that use of other medications was measured, all nine studies reported that the number of patients using medications or the total quantity of medications decreased from baseline to longest follow-up. Notably, two studies reported that pump recipients used no oral or transdermal medications at all. For a summary of the findings of all nine studies, refer to Table 47 of Appendix D.

Change in Dose of Infused Medication

The dose of medication infused by an implantable infusion pump increased over time, but the amount of dose change is not predictable from available studies.

Ten studies that enrolled a total of 218 patients reported dosage at one or more long-term treatment follow-up time. We did not rate the strength or stability of this conclusion because of the confounding influence of factors including titration, differences in prescribing preferences, progression of underlying disease, and unclear causal relationship between pain levels and quantities of medication. Eight studies reported doses of morphine or morphine equivalent/equianalgesic dose, one study reported on dosing of methadone, and one reported on dosing of sufentanil.

All studies reported increases in drug administered after baseline. No conclusions can be drawn regarding dose escalation associated with methadone or sufentanil, as only one study addressed each of these drugs. The remaining text in this section will pertain to the eight studies that reported using morphine or a morphine-equivalent dose. Five of these studies only reported baseline and one follow-up time, so the changes in the quantity of intrathecal opioid administered appears to be increasing linearly, although that may not actually be the case. The two studies with more than three time points show a dosage increase pattern that plateaus. The dose of drug administered at baseline or last recorded follow-up time do not appear to be related to mean VAS.

Question 2. What is the safety profile of implanted infusion pumps?

Discontinuation from Clinical Study due to Adverse Events

Of patients with CNCP who begin intrathecal opioid therapy with an implanted pump, 8.3% (95% CI 4.4% to 15.1%) patients discontinued participation in the clinical study due to adverse events and effects. (Stability of estimate: Low).

Seven studies (n = 132) on intrathecally-administered opioids reported the number of patients who discontinued participating in case series due to adverse events. Drugs administered included morphine alone, morphine with or without bupivacaine or clonidine, or with sufentanil citrate or fentanyl as an alternative. Patients had pain due to various or unspecified causes in four studies, failed back surgery syndrome in three studies, and neuropathic pain alone in one study. In one study, only some pump candidates had an infusion trial, and in two no candidates underwent a trial. The median internal validity score of this evidence base was within the low range.

Zero to 15% of patients per trial discontinued treatment due to adverse events. Zero to two patients discontinued per trial, with study sizes ranging from 11 to 30 patients enrolled. We combined these studies in a meta-analysis; no substantial heterogeneity was detected (I^2 <0.001). At longest duration of treatment (six months — mean of 29 months), 8.3% (95% CI 4.4% to 15.1%) patients discontinued participation in intrathecal treatment studies. All sensitivity analyses were robust. When only the studies that used an infusion trial on all pump candidates were analyzed, the proportion of patients who discontinued due to adverse events was not substantially different from other studies.

Adverse Events

No serious drug-related adverse events or effects were reported by the clinical trials. However, serious pump-related events, primarily reoperation due to pump technical failure, were reported. Determining the rates of adverse events was not possible due to differences in reporting among studies.

Patients enrolled in the studies that reported adverse events were being treated for CNCP due to various causes, failed back surgery syndrome, neuropathic pain, or osteoporotic vertebral fracture. Morphine was prescribed in eight studies, with or without an additional drug such as bupivacaine, midazolam, or clonidine. Alternative drugs administered were administered in some studies, including sufentanil citrate, fentanyl, hydromorphone, or methadone. In the study that did not administer morphine, methadone was administered. One study did not report drug administered.

We divided the adverse events into two general categories: drug-related and device-related. The most commonly reported drug-related adverse events included gastrointestinal effects (e.g., constipation, nausea, dyspepsia), headache, fatigue/lethargy/somnolence, and urinary complications (e.g., retention, hesitancy, “disturbance”). No apparently life-threatening opioid-related adverse events, were reported. It is not possible to determine from the publications the severity of many adverse events such as headache or nausea, or whether adverse events and effects were successfully managed medically or whether they abated over time with acclimation to the drug. Only one patient with a symptom suggestive of opioid addiction, drug-seeking behavior, was reported.(6)

Device-related adverse events included pump and catheter malfunctions and malpositioning, surgical complications, and post-surgical complications. Where reported, the percentage of patients who required reoperation for device complications during the follow-up period ranged from 9% to 42%.

In addition, seven deaths were reported in three studies. In one study, a patient died during elective coronary angioplasty.(7) In the second study, one patient died due to suicide, another due to myocardial infarction, and a third due to unknown cause.(8) It is unclear whether the suicide or death due to unknown cause was possibly pump- or opioid-related. In the third study, one patient died due to chronic obstructive pulmonary disease, another died due to pericolonic abscess, and a third died due to myocardial infarction, none of which were considered treatment-related.(6)

A total of 975 relevant reports were identified in the Manufacturer and User Facility Device Experience Database (MAUDE) database. Although the majority of the reports were on non-serious events and effects, many serious events and effects, including paralysis and death, were reported.

An unfiltered search of the FDA MAUDE database yielded 9,082 reports. ECRI Institute applied several filters to identify the most relevant reports (for example, filtering for any mention of "intraspinal"or "intrathecal" or other spine-related term; see Appendix A for more details); a total of 975 relevant reports were identified. However, because the number of people who have received an implantable pump in the United States is unclear, determining the *rates* of these events is not possible. Determining whether some of the events were due to the pump or its use (e.g., human error), or due to the underlying painful condition or a co-morbid disease, was not always possible. In addition, the severity or duration of events was not always reported, and whether events were successfully managed medically or surgically was not always reported. Importantly, these reports are on the use of implantable infusion pumps for any indication, including cancer pain and spasticity. Implanted infusion pumps may have different harms profiles in different patient populations, and these findings should not necessarily be generalized to patients with CNCP.

We divided the event reports by patient health outcome (e.g., infection, edema, insufficient pain relief) and device-related events (e.g., pump or catheter failure, surgical error during implantation). We used the term 'health outcome' to label the category of health effects that may be caused by drug administered because it was not always possible to definitively attribute the effect to a drug. In many instances, more than one event was described in a report, and more than one event occurred per patient. For this reason, the number of events in our tables total to more than 975.

Most importantly, 53 deaths were reported. Most frequently, in 15 cases, the deaths were due to unknown causes. The other most common reported causes were cardio/pulmonary arrest (seven cases), cardiac disease (five cases), and overdose (five cases). Causes of death and number of reports are listed in Table 54 of Appendix D.

The highest number of serious and potentially serious reports cited infection (128 reports), inflammatory mass(es) (83 reports), and paralysis (20 reports). The most frequently reported device-related event was re-operation due to pump or catheter failure (405 reports), followed by removal of the device without replacement (211 reports). All other device-related events had fewer than 100 instances, and included non-operative equipment revision (86 reports), operator error (e.g., incorrect pump programming) (35 reports), and planned device replacement due to battery expiration (26 reports).

Question 3. Is there any evidence of differential efficacy or safety issues amongst special populations?

No conclusions can be drawn regarding differential efficacy or safety of implantable infusion pumps among different patient populations due to an absence of evidence.

None of the included case series investigated whether certain patient characteristics were related to the efficacy or safety of implantable infusion pumps. We used meta-regression techniques in an attempt to identify such relationships, but none were statistically associated. The small size of the evidence base may explain the lack of significant findings. No additional literature addressing this key question was identified.

Table 2. Summary of Effectiveness and Safety Findings

Outcome		k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Pain	Continuous	7	143	Low	89.2%	SMD	2.34 (1.46-3.24)	Yes	Weak	No	Unstable	Drug infusion with an implantable pump leads to clinically significant pain relief in patients with CNCP. (Strength of evidence: Weak). No quantitative conclusion drawn due to differences among studies.
	≥25% Pain Relief	6	123	Low	66.5%	Proportion	56.3% (33.7%-73.3%)	NA	Weak	No	Unstable	No quantitative conclusion drawn due to differences among studies.
	≥50% Pain Relief	7	150	Low	67.6%	Proportion	40.8% (25.2%-58.5%)	NA	Weak	No	Unstable	No quantitative conclusion drawn due to differences among studies.
Discontinuation from Clinical Study due to insufficient pain relief		5	102	Low	<0.01%	Proportion	8.0% (3.8%-15.8%)	Yes	Weak	No	Low	Of patients who began treatment with an implantable pump used for intrathecal opioid delivery for CNCP, 8.0% (95% CI 3.8%-15.8%) discontinued treatment in the clinical trial due to insufficient pain relief. (Stability of evidence: Low)

Outcome	k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Quality of Life	2	48	Low	-	-	-	No	Inconclusive	-	Unstable	It is not possible to determine whether long-term use of intrathecal opioids change the quality of life for patients with CNCP, because the two studies that met inclusion criteria for this outcome had inconsistent findings (one found improvement, but the other did not)
Functional Status	1	24		-	-	-	No	Inconclusive	-	Unstable	Because only one study reported this outcome, there was an insufficient quantity of evidence to permit a conclusion for this outcome.
Employment Status	4	83	Low	36.7%	Odds Ratio	-	No	Inconclusive	No	Unstable	The current evidence is insufficient to determine whether implantable infusion pumps are associated with a change in employment status among patients with chronic non-cancer pain.
Use of other medications and other treatments	9	347	-	-	-	-	Yes	-	-	-	Intrathecal administration of opioids by implantable pump was associated with an overall decrease in the quantity of other drugs taken or a decrease in the proportion of patients taking other drugs.
Changes in quantity of infused medication administered	10	218	-	-	-	-	Yes	-	-	-	The dose of medication infused by an implantable infusion pump increased over time, but the amount of dose change is not predictable from available studies.

Outcome	k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Discontinuation from Clinical Study due to adverse events	7	132	Low	<0.01%	Proportion	8.3% (4.4%-15.1%)	Yes	NA	Yes	Low	Of patients with CNCP who begin intrathecal opioid therapy with an implanted pump, 8.3% (95% CI 4.4% to 15.1%) patients discontinued participation in the clinical study due to adverse events and effects. (Stability of estimate: Low).
Adverse Events (Clinical Studies)	13	231		-	-	-	-	-	-	-	No serious drug-related adverse events or effects were reported by the clinical trials. However, serious pump-related events, primarily reoperation due to pump technical failure, were reported. Use of meta-analysis to determine the rates of adverse events is not possible due to differences in reporting among studies.
Adverse Events (MAUDE)	NA	NR		-	-	-	-	-	-	-	A total of 975 relevant reports were identified in the Manufacturer and User Facility Device Experience Database (MAUDE). Although the majority of the reports were on non-serious events and effects, many serious events and effects, including paralysis and death, were reported.

CI Confidence interval.
k Number of studies.
n Number of patients for whom the outcome was analyzed.
NA Not applicable.
NR Not reported.
SMD Standardized mean difference.

Question 4. What are the cost implications and cost effectiveness for implantable infusion pumps?

The available evidence is insufficient to determine whether the long-term costs of implantable infusion pumps are different from the long-term costs of non-pump treatment in the management of chronic non-cancer pain.

Four cost analyses are discussed in this section: three of these were identified by searches, and the fourth was an unpublished analysis provided to us by the Washington State Health Technology Assessment Program. Two of the published articles described five-year cost analyses of implantable infusion pump treatment for failed back surgery syndrome (FBSS): one was a cost-effectiveness analysis in the U.S. in 1997 that used data from the literature and an expert panel,(9) and the second was an actual cost study in Canada in 2000.(10) The third published article was a six-month randomized trial published in 2003 comparing different methods for selecting patients for implantable infusion pumps (a screening trial with intrathecal injection, or a screening trial with epidural infusion).(11) The unpublished analysis was commissioned by Medtronic, Inc. (the manufacturer of SynchroMed® infusion systems) and prepared by Reden & Anders (an actuarial firm in Eden Prairie, Minnesota).(12) Using claims data from 2003-2006, authors estimated the budgetary impact of covering intrathecal drug delivery systems on the Medical Aid Budget of the Washington State Department of Labor and Industries.

An overall summary of the three long-term analyses appears in Table 3 below. Subsequently, all four analyses are discussed individually, and then an overview section summarizes our findings.

Table 3. Overview of the Three Long-term Cost Analyses

Cost analysis	Primary methods*	Primary results*
De Lissovoy et al. (1997)(9) **Country**: USA **Type**: CEA model **Timeframe**: 5 yrs	**Patients**: Chronic pain due to FBSS. **Comparison**: Pump vs. non-pump **Data source(s)**: Expert opinion and the published literature **Assumptions**: Initial implant and fees $22,495; pump replacement $15,897; (other costs also; see tables in main text). Major postsurgical complication rate of 2.7%; major long-term complication rate of 7.2%. Pump failure rate increasing from 0% in the first year to 75% within five years. Elective removal of the pump in 3% of patients annually. For non-pump treatment, annual charge of $4,847 for medications, and $5,634 for hospital admissions for uncontrolled pain (other costs also; see tables in main text). 5% annual discount rate. For pain relief, the typical pump patient would have 3.65 of the five years with good/excellent pain relief, whereas the typical non-pump patient would have no years with good/excellent pain relief. **Sensitivity analyses**: Best-case analysis assumed lower adverse event rates and lower costs of pump treatment; worst-case analysis assumed the opposite. **Funding source**: A contract between Medtronic Inc. and the Battelle Memorial Institute	**Base case.** Total five-year cost of pump treatment was $82,893 in 1997 dollars. For non-pump treatment it was $85,186 (statistical test not reported). **Best case**: Total five-year cost of pump treatment $53,468 in 1997 dollars. **Worst case:** Total five-year cost of pump treatment $125,102 in 1997 dollars. **Estimated time to cost neutrality for the base case:** 1.8 years.
Kumar et al. (2002)(10) **Country**: Canada **Type**: Cost outcomes in an RCT **Timeframe**: 5 yrs	**Patients**: Chronic pain due to FBSS. **Comparison**: Pump (N = 23) vs. non-pump (N = 44). Pump patients had first responded favorably to a screen with intrathecal morphine, but no such selection occurred in the non-pump group. **Data source(s)**: Actual costs incurred; fee schedules from Saskatchewan; pump list price for Canada; pharmacotherapy costs according to the Saskatchewan Health Formulary **Assumptions**: That the differential screening of patients would not bias the results. Initial pump implantation and fees $23,270. All pumps replaced after four years. For the pump group, no hospital admissions for breakthrough pain, and no adjunctive therapies necessary (except for pharmacotherapy for pain flare-ups and pump refills) (other costs also; see main text). For the non-pump group, 15 annual hospital admissions for breakthrough pain, and adjunctive therapies necessary (other costs also; see main text). **Sensitivity analyses**: Best-case analysis was restricted to the 9 pump patients who did not experience any complications; worst-case analysis was restricted to the 14 pump patients who experienced at least one complication. **Funding source**: Not reported, but authors stated that they have "no financial interest in the	**Base case.** Total five-year cost of pump treatment was $43,508 in 2000 U.S. dollars. For non-pump treatment it was $56,257 (statistical p value 0.028 when compared to pump treatment). **Best case**: Total five-year cost of pump treatment was $41,811 in 2000 U.S. dollars **Worst case:** Total five-year cost of pump treatment was $46,052 in 2000 U.S. dollars **Estimated time to cost neutrality for the base case:** 2.3 years.

Cost analysis	Primary methods*	Primary results*
	subject under discussion."	
Reden and Anders (2006)(12) **Country**: USA **Type**: Cost model **Timeframe**: 30 yrs	**Patients:** Diagnoses not reported; probably included CNCP and other diagnoses. **Comparison**: Pump vs. non-pump **Data source(s)**: Ingenix Inc.; Washington L&I fee schedules and inpatient and outpatient reimbursement for 7/1/06; pharmacotherapy costs at standard costs plus dispensing fee **Assumptions**: That not receiving the pump would incur the same monthly costs as costs incurred in the single month prior to receiving the pump ($4,055 per month). Pump replacement every 7 years; some incidents of earlier pump replacement did occur and were incorporated. "Method 1" assumed no ongoing cost savings from the pump, whereas "Method 2" assumed savings (see main text). Trend assumptions included 13% annual billed charge trend; annual net medical trends decreasing from 10% for year 1 to 4% for years 6 through 30; 3% annual discount rate. **Sensitivity analyses**: Three types: 1) pump replacement every 5 years, or every 9 years; 2) net annual medical cost trend +1% from base case or -1% from base case; 3) annual discount rate 2% or 4%. **Funding source**: Medtronic, Inc.	**Base case:** Non pump 30-year total cost was $2,005,905 per patient. Pump 30-year total cost using Method 1 (assumed no cost saving from implantation) was $2,181,348 per patient. Pump 30-year total cost using Method 2 (assumed cost saving from implantation) was $1,542,581 per patient. **Sensitivity analysis of timing of pump replacement:** Replacement every 5 years meant an annual pump vs. no-pump difference of $19,026 for Method 1 (favoring non-pump) and -$7,485 for Method 2 (favoring pump). Replacement every 9 years meant an annual pump vs. no-pump difference of $4,582 for Method 1 (favoring non-pump) and -$15,012 for Method 2 (favoring pump). **Other sensitivity analyses**: see main text. **Estimated time to cost neutrality for the base case:** 1.5 years using Method 2 (neutrality analysis not performing using Method 1).

CEA Cost effectiveness analysis
FBSS Failed back surgery syndrome
RCT Randomized controlled trial

* Many more details about these cost analyses appear in the main body of the report. The fourth included cost analysis(11) is not listed in this table because it was only for six months, as opposed to 5+ years in the analyses above.

Economic Model of Five-year Pump Treatment for Failed Back Syndrome

de Lissovoy et al (1997)(9) devised a model to compare pump use to non-pump use in patients with failed back surgery syndrome. Costs in 2008 are likely higher than those analyzed in this 1997 report, but this may be true for both pump use and non-pump use. Thus, the *comparative* cost information in the model may still be relevant. However, pump-specific costs may have changed over the years, which would mean that these results are difficult to apply to today's medical decisions.

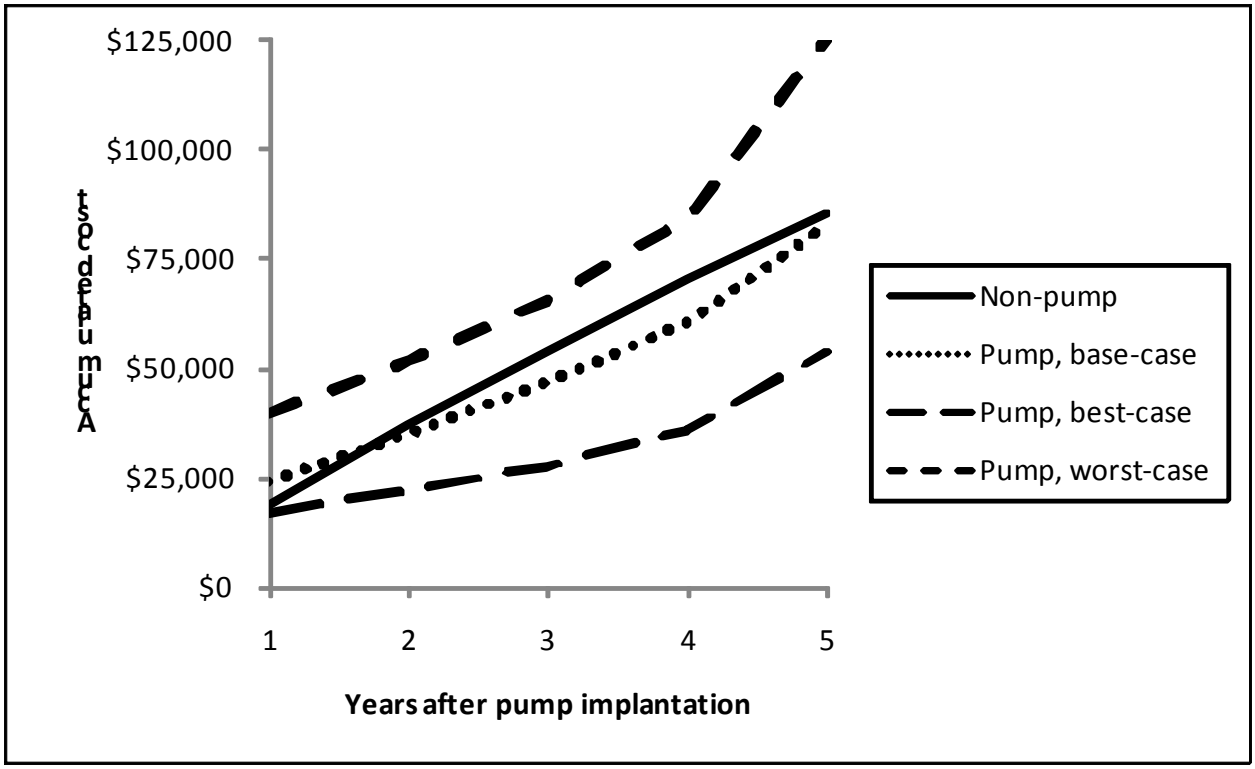
Over a five-year period, given various assumptions about costs and probabilities, authors calculated that pump treatment would cost a total of $82,893 for the base-case analysis. This was slightly less than the five-year cost of non-pump treatment (which was $85,186; statistical test not reported). These five-year estimates were for 1997-2001. Based on 3% annual inflation, the total costs translate in 2008-2012 dollars to $114,743 for pump therapy and $117,917 for non-pump therapy.

Authors performed two types of sensitivity analyses of their assumptions concerning the costs of pump use: one was a best-case analysis (employing lower fees for screening, implantation, physician charges, adverse event rates, as well as lower complication rates and later needs for pump replacement), and the other was a worst-case analysis (employing higher fees, higher complication rates, and earlier pump replacement). In the best case, accumulated five-year pump cost was $53,468, whereas in the worst case it was $125,102. Again, these figures were for 1997-2001; 3% annual inflation increases the two figures to $74,012 and $173,170, respectively.

Translating these results to cost-effectiveness, authors computed the cost per year of pain relief for implantable infusion pumps vs. non-pump therapy. This cost was estimated to be $624 lower for implantable infusion pumps than for non-pump therapy. In the best-case scenario it was $7,832 lower, and in the worst case scenario, it was $12,276 greater. These calculations assumed that during the five years after pump implantation, patients would experience 3.65 years with good/excellent pain relief in the base case, 4.05 years in the best case, and 3.25 years in the worst case.

Authors noted that the pump involved greater up-front costs, but these were eventually offset by the greater long-term costs of non-pump treatment (see Figure 2 below). The time at which accumulated costs for pump (base case) and non-pump treatment were equal (i.e., the crossover point) was 1.8 years.

Figure 2. Accumulated Five-year Costs of Treating Failed Back Syndrome Surgery with Non-pump Treatment or Pump Treatment, based on de Lissovoy et al. (1997)



Actual Analysis of Five-year Pump Treatment for Failed Back Syndrome

The second five-year cost analysis of pump vs. non-pump treatment for FBSS was based on actual cost data and was conducted in Canada (year 2000).(10) Eighty-eight patients were randomized into two equal-sized groups: one group was screened for suitability for an implantable infusion pump, whereas the other group received conventional pain therapy. During the pre-implantation screening, only 23/44 patients in the pump group responded favorably to intrathecal morphine, and remained in the trial, whereas the 21 nonresponders were then excluded. Therefore, the analysis compared a) the cost of intrathecal administration among those who had a successful screening trial (N = 23) vs. b) the cost of conventional pain therapy among those who may or may not have had a successful screening trial (N = 44).

One problem with this design is that some patients may be hard-to-treat *in general*, regardless of treatments attempted. Excluding such patients from one group, but leaving them in the other group, introduces a bias in favor of the first group. The authors argued that an explanted pump (or a sham pump) would have been unethical. This may be true, but the point remains that differential exclusion of nonresponders makes it more difficult to interpret the study results.

For the 23 patients who received the implantable infusion pump, the average per-patient five-year cost was $43,508 USD. By comparison, the average five-year cost of conventional pain treatment (CPT) among the 44 patients who received this strategy was $56,257 USD (a statistically significantly higher cost; p = 0.028). Authors also performed best-case and worst-case analyses for pump treatment. The best-case analysis was restricted to the nine patients who did not have any complications during the five-year period; their average five-year accumulated cost of implantable infusion pump use was $41,811. The other 14 patients all experienced at least one complication, and they comprised the worst-case analysis; their average five-year accumulated cost of implantable infusion pump use was $46,052.

What explains the greater five-year cost in conventional pain management as compared to implantable infusion pump use? One possible answer is the greater need for supplemental treatments, which includes hospital admissions and ER visits for breakthrough pain, as well as adjunctive therapies such as physical therapy (see Table 20 and Table 21). In the implantable infusion pump group, no patient required such interventions. By contrast, in the conventional pain management group, an average of $35,266 was required for these purposes, representing 63% of the five-year cost. However, recall that the conventional group was not prescreened for response to intrathecal administration. Based on the reported data, one cannot determine the cost of non-pump treatment among patients who would have responded to intrathecal administration.

As with the U.S. CEA, the Canadian authors concluded that the greater upfront costs of the pump are eventually offset. They found a crossover point at 2.3 years, and sensitivity analyses found crossover points ranging from 2.2 years to 2.8 years.

Kumar also compared rates of disability and return to work. As measured by the Oswestry Disability Index (ODI), the average five-year improvement among those who received the pump was 27%, whereas the other group improved an average of 12%. For return to work, the authors stated that in the pump group "two patients who had been working with intermittent time loss prior to implantation continue to work with increased comfort and without any disruptions." Also, two additional patients in that group "were unemployed before undergoing implantation and have been able to take up part time employment". By contrast, in the non-pump group, no patients returned to work during the five-year study period.

Six-month Randomized Trial

In a small trial, authors compared the cost of screening for pump use with intrathecal injection (18 patients, all with FBSS) vs. screening for pump use with epidural infusion (19 patients, all with FBSS) (study funding by Medtronic, Inc.).(11) Twelve of the 18 screened using intrathecal injection (67%) reported at least 50% pain relief on two consecutive ratings, and subsequently received an implantable infusion pump. The other six patients did not receive a pump; authors did not report what treatment they did receive. Fifteen of the 19 screened using epidural infusion (79%) reported at least 50% pain relief on two consecutive ratings, and subsequently received an implantable infusion pump. Treatment was not reported for the other four patients.

Screening with intrathecal injection was much less expensive ($1,862 in 2003 U.S. dollars) than screening using epidural infusion ($4,762; statistical test $p < 0.0001$). The cost of the pump and implanting it was approximately $20,000. Authors also noted that the screening trial took significantly shorter with intrathecal injection (median one day) than epidural infusion (median two days). The hospital stay itself was also shorter in the intrathecal injection group. This may have been partially due to the need for catheter placement in the OR for the epidural infusion group; whereas no OR visits occurred in the intrathecal injection group. The two groups did not differ on other reported costs such as clinical visits, physician visits, or visits to other healthcare professionals. No other cost data were reported.

Reden & Anders Analysis

We also summarized a cost analysis(12) by the actuarial firm Reden & Anders, which was commissioned by Medtronic, Inc. This analysis utilized insurance claims data to estimate the budget impact to the Washington State Department of Labor and Industries (L&I) of covering intrathecal drug delivery systems. The analysis likely included patients who did not have chronic noncancer pain as their primary diagnosis. Also, authors estimated a much higher cost of non-pump treatment than the other cost analyses we examined, and furthermore they assumed that pumps would need replacement every seven years rather than every ~four years as assumed by other cost models. Although the Reden & Anders analysis addressed intrathecal drug delivery and was tailored to Washington State L&I, it was not focused on chronic, noncancer pain, and therefore its conclusions are less relevant to this report. Text and tables in the main body of the report contain the findings and conclusions of this analysis.

Cost Overview

In general, we deemed the evidence insufficient to determine whether long-term costs of implantable infusion pump treatment are different from those of non-pump treatment. Our reasons for this determination are described next.

The de Lissovoy analysis(9) was conducted at least 11 years ago using simulated patients within a deterministic Markov model, and more advanced methods are now available for more accurate cost analysis. Authors did incorporate many important costs, including pump replacement and adverse events, and the estimated five-year total costs for the two treatments were very similar ($82,893 for the pump vs. $85,186 for non-pump). However, sensitivity analyses revealed very wide ranges for pump treatment (from $53,468 to $125,102). This wide range of uncertainty casts doubt on any conclusion about comparative long-term costs.

The Kumar analysis(10) was conducted in Canada eight years ago. Canadian costs structures are quite different from those in the US. Also, interpretation of the study results was complicated by the differential selection of patients in one group but not the other, which may have biased the study to find lower costs in the pump group. These two issues meant that we did not draw conclusions based on its results.

The other two analyses were also judged inconclusive for long-term comparative costs for chronic non-cancer pain. The Anderson trial(11) focused on the costs of different screening methods for the pump, rather than costs of pump vs. non-pump treatment. The Reden and Anders analysis may have included patients without chronic non-cancer pain, so its precise relevance is unknown. Also, authors attempted to estimate the cost of non-pump treatment using costs incurred in the single month prior to pump implantation. This latter cost (about $4,000 per month) was much higher than the costs reported in the other analyses (about $1,000 per month), calling into question any comparison with pump treatment costs.

Summary

The only kind of evidence about whether implantable infusion pumps are effective for patients with chronic noncancer pain comes from uncontrolled case series, which are less rigorous clinical studies than controlled trials and therefore may yield less reliable conclusions.

On average, patients in case series reported considerably less pain after the implantation of an infusion pump. It was not possible to determine precisely how much pain relief the average patient had due to inconsistency in average pain relief among studies. While some individuals attained meaningful levels of pain relief, some did not. It was not possible to determine precisely what percentage of patients did or did not attain meaningful pain relief due to inconsistent findings among studies. Although four studies reported an increase in the proportion of patients who could work after pump implantation, this finding was not statistically significant for all studies or when the studies were pooled; therefore, no conclusion was drawn. Quality of life and functional status were too sparsely reported to permit conclusions. Dose of infused drug tended to increase over time, while use of other medications decreased; however, the reasons for these changes were unclear. Many minor adverse events and some device-related events requiring surgical intervention occurred in the case series. Serious drug- and device-related adverse events, including death, were identified in the MAUDE database and in FDA recalls and Medtronic safety alerts; however, the actual rate of these events is unknown.

No included studies attempted to identify patient factors related to harms, efficacy, or drop-out. No factors were identified in our own statistical analysis, but this may be due to the limited number of studies available and sparse reporting. Studies designed to examine patient- and treatment-related factors predicting long-term success with opioid therapy would be extremely useful for optimum patient selection. Potentially meaningful prognostic factors could include baseline severity and cause of pain, co-morbidities, general health, and motivation to improve.

For costs, due to uncertainty in the reported results from four analyses, we deemed the evidence insufficient to determine the comparative long-term costs of pump and non-pump treatment of chronic noncancer pain.

Introduction

Chronic Pain

Diagnosis of Chronic Pain

The International Association for Study of Pain (IASP) defines chronic pain as pain lasting beyond the normal time of healing, defined as three months or longer.(1) Diagnosis of chronic pain is made based on patient report of the duration of pain. In the IASP system, chronic pain is described based upon its characteristics: the bodily region(s) affected, the bodily system(s) involved, the temporal pattern, the intensity of the pain, and the underlying etiology of the pain.

Etiology

Chronic noncancer pain (CNCP) can result from any number of disorders, such as arthritis, postherpetic neuralgia, phantom limb pain, or pancreatitis. The most common source of chronic pain is low back pain,(13-15) which can be the result of injury or disease.

Noncancer is often broadly categorized as nociceptive pain, neuropathic pain, or both. Nociceptive pain results from "injury or inflammation of somatic or visceral tissue."(16) An example of noncancer nociceptive pain is deep, aching musculoskeletal pain. Neuropathic pain results from "neuronal maintenance of pain either peripherally or in the central nervous system."(16) An example of neuropathic pain is sharp and shock-like pain due to diabetic neuropathy. Patients may have both nociceptive and neuropathic pain due to one etiology producing both types of pain, such as failed back surgery syndrome (FBSS), or more than one painful condition. Some patients may have painful conditions that cannot be easily categorized as neuropathic and/or nociceptive pain.(17)

Epidemiology

Chronic pain is an important and common medical concern worldwide. A systematic review of four international studies conducted in developed countries found prevalence rates of any type and severity level of chronic pain ranging from 10.5% to 55.2% of the population.(18) The Pain in Europe survey of 46,000 people showed that one in five individuals reported suffering from chronic pain. In this survey, chronic pain sufferers reported seven years of chronic pain on average, with some reporting pain lasting more than 20 years.(19) A World Health Organization (WHO) survey of primary care patients seeking care at 15 centers in 14 countries across Asia, Africa, Europe, South America, and North America found that 22% of primary care patients reported pain lasting longer than six months.(15) An estimated 9% of Americans(20) and 19% of Europeans(19) have moderate to severe CNCP.

Risk factors for chronic pain include demographic and genetic factors. In general, older individuals and women are more likely to experience chronic pain.(19,21-23) Individuals with a family history of CNCP may also be more likely to develop chronic pain, possibly due to central nervous system anomalies.(24) Additional risk factors vary by the underlying cause of pain.

Natural History

Acute pain commonly resolves completely within six weeks, even without treatment. However, some conditions, including diabetic neuropathy and failed back surgery syndrome, are associated with continuous pain without relief. Other causes of chronic pain, including lupus and rheumatoid arthritis, tend to cause pain episodically (periods of pain may be intervened by periods of relief due to periodic remission of the disease).

Most cases of chronic pain should not be expected to spontaneously resolve permanently, and a persistent or progressive underlying cause of pain may make complete recovery unlikely. A follow-up study of patients treated for CNCP found that, after ten years, only 2.5% of patients fully recovered.(25)

Treatment

According to clinical practice guidelines, treatment goals should be individualized depending on each patient's particular situation. Underlying cause of pain, comorbidities (which many chronic pain patient suffer from), and patient's desired activity level could all affect treatment goals.

There are many conservative treatments for chronic noncancer pain, which should be selected based upon the cause and severity of the patient's pain. Conservative treatments are often prescribed in combinations. Conservative treatments for chronic noncancer pain include but are not limited to:

- Correction of underlying disorder when possible, such as glucose control for diabetic neuropathy
- Simple analgesics, typically administered orally
- Co-analgesics or adjuvant therapy (e.g., antidepressants, anticonvulsants)
- Opioid and opioid compound analgesics, typically administered orally or transdermally
- Physical therapy
- Trigger point injections
- Steroid injections
- Massage
- Acupuncture
- Cognitive behavioral therapy

For the treatment of cancer pain, the World Health Organization (WHO) recommends a three-step analgesic ladder: (1) orally administered nonopioids first, (2) weak opioids if needed, and (3) strong opioids if needed. WHO states that the goal of stepwise opioid treatment for cancer patients is to achieve complete freedom from pain.(26)

However, pain elimination is not recommended by some experts as a goal of therapy for patients with CNCP who are taking opioids (which can be administered by an implantable infusion pump). The College of Physicians and Surgeons of Ontario recommends "achievement of tolerable pain and/or improvement of function" as a goal.(27) Guidelines from the College of Physicians and Surgeons of Alberta(28) and the College of Physicians and Surgeons of New Brunswick(29) recommend two goals for the treatment of chronic nonmalignant pain: "enhanced function (broadly defined to include physical, psychological and social function) and improved comfort." The National Pharmaceutical Council and the Joint Commission recommend very similar goals for treatment of CNCP.(30)

Implantable Infusion Pumps

Underlying Theory

Implantable pumps are devices fully surgically implanted into the patient to provide round-the-clock long-term drug therapy. Implantable infusion pumps are reserved for patients with chronic pain who are (1) ineligible for corrective surgery, (2) need round-the-clock pain relief, and (3) for whom conservative medications and treatments offered insufficient pain control and/or unacceptable adverse events. Implantable pumps may also confer greater drug accountability and compliance than other modes of drug administration, as clinicians can program the device's drug dispensing schedules and the patient does not need to administer the drugs to himself.(31) These proposed advantages make implanted infusion pumps

a treatment option even when means of systemic drug delivery (e.g., pills, patches) have failed due to insufficient pain relief or intolerable adverse events.

Because medications are delivered directly to the desired site, pain control is theoretically optimized while adverse events associated with systemic administration are minimized because the overall drug dose is reduced. Conversion ratios approximate 300 mg oral morphine to 10 mg epidural morphine to 1 mg intrathecal morphine.(32) Dose is reduced because delivery directly to the spine, where opioid receptors are located, bypasses systemic metabolism of the drug.(33) Opioids administered to the intrathecal space of the spinal cord enter the spinal cord and dura mater and then the epidural space, where they bind receptors in the white matter and in the dorsal horn and are taken up in fat and subjected to venous uptake that takes them to the plasma compartment.(34) Hydrophilic opioids (e.g., morphine) have less binding to fat in the epidural space and to nonspecific receptors in the white matter than lipophilic drugs (e.g., fentanyl, sufentanil), so their transfer to systemic circulation is slower, and resultantly the onset of analgesia of hydrophilic opioids is slower and longer-lasting.(34) Because of these physiological interactions, the more hydrophilic an opioid is, the more potent it is in spinal administration.(35) Hydromorphone is of intermediate lipophilicity.(34,35)

Basic Procedure

Candidates for an implantable infusion pump typically undergo a screening trial before receiving a long-term implanted pump. These trials are intended to identify the patients who may benefit from an implanted pump. Trials temporarily administer the drug planned for use to the site of interest using external injections or external infusion pumps. Only patients who have a successful trial, typically defined as at least 50% pain relief and no unacceptable adverse events, subsequently receive an implanted pump. In early case series of intrathecal opioid administration, trials could be as short as a single bolus of drug. More recent clinical trials fit the patient with a catheter attached to an external pump, and the duration of the trial lasts from several days to two weeks. The trial may be conducted on an inpatient basis.

After a satisfactory trial, patients can receive an implantable infusion pump. The pump is surgically implanted under general anesthesia. The pump is typically implanted through an abdominal incision into a surgically-created pocket.(36) For intraspinal use, the pump itself is implanted subcutaneously under the infraclavicular fossa or in the abdominal wall. The catheter, which delivers drugs from the pump to the site for administration, is then subcutaneously tunneled from the pump or reservoir pocket to the back incision, where it is connected to the spinal catheter.

The catheter can be placed to deliver drugs to an intravenous, intraarterial, subcutaneous, intraperitoneal, intrathecal, epidural, or intraventricular site. ‘Intraspinal’ delivery can refer to epidural and/or intrathecal delivery. Intrathecal infusion is the main use of the pump in the studies included in *Results Synthesis*. For intrathecal administration, the pumps deliver medications directly to the spinal fluid of the intrathecal space of the spine, where the medications can act locally on pain receptors to disrupt transmission of pain signals.(37)

Placement of the catheter needle is usually performed under fluoroscopic guidance. The catheter is inserted through the needle and advanced until it reaches the appropriate position. The needle is removed and the catheter is anchored to the supraspinous fascia. Proper catheter placement and anchoring helps prevent kinking or migration of the catheter. After the unobstructed flow of cerebrospinal fluid through the catheter is confirmed, the catheter is connected to the pump. The pump is secured in place, and surgical wounds are irrigated and closed.

The patient typically spends at least the night following implantation in the hospital. Sutures are removed in a post-surgical visit seven to ten days after implantation. When the drug supply is depleted, the pump can be refilled in a doctor’s office using a needle injection through the pump’s self-sealing septum. Frequency of refills depends on the infusion rate, but may range from two to six months.

Several classes of drugs can be infused into the spinal cord for relief of chronic pain, including opioids, local analgesics, ziconotide, and baclofen. Morphine is most commonly used and is the only opioid approved by the United States Food and Drug Administration (FDA) for intrathecal use. A newer nonopioid drug, ziconotide, is a calcium channel blocker that is also approved by the FDA for intrathecal drug administration when intrathecal morphine is insufficiently effective or produces unacceptable side effects. Baclofen is an antispastic drug approved by the FDA for oral or intrathecal treatment spasticity or dystonia, but was used in a study in the synthesis portion of this report to relieve pain in a small number of patients. Additional drugs, especially opioids, are commonly used off-label in intrathecal pumps. Hydromorphone is considered another opioid of choice by some, although there may be an increased risk of granuloma associated with administration of hydromorphone at high doses.(17) As a second line of treatment, bupivacaine (a local anesthetic) or clonidine (an adrenergic agonist) may be added to the morphine or hydromorphone, or, as a third line, both. These combinations may be particularly helpful for treating neuropathic pain.(38) Other, less commonly used opioids include hydromorphone, fentanyl, methadone, sufentanil, and meperidine.

Patient Indications and Contraindications

Indications

Reported indications for treatment of CNCP by implantable infusion pump include:(35)

- Definable cause of pain
- Surgically-correctable pathology excluded
- Less complex and less invasive therapies have failed or have unacceptable side effects, usually including oral and transdermal opioid therapy
- Passed a psychological evaluation
- No medical contraindications to surgery for pump implantation
- Requiring constant pain control
- Successful infusion trial (described above)
- Lack of placebo response. Clinicians may also fill pumps with saline to determine whether a candidate responds to the placebo; placebo responders do not receive a long-term pump for intrathecal drug delivery. However, other clinicians believe placebo trials are unethical.(38)

No publications that report differential pain relief in patients with different underlying causes of pain were identified. Possible painful conditions for which spinal drug delivery may be appropriate include (but are not limited to):(35)

- Arachnoiditis
- Axial spinal pain
- Brachial plexitis
- Central pain syndromes
- Complex regional pain syndrome
- Diffuse pain
- Failed back syndrome
- Failed spinal cord stimulation
- Neuropathic pain or peripheral neuropathy
- Post-stroke pain
- Spinal cord injury pain

Contraindications

Absolute and relative contraindications to infusion with an implantable pump identified in the literature include:

- Drug allergy or hypersensitivity: Drug allergy is an absolute contraindication for the drug to which the patient is allergic,(39) but not necessarily a contraindication to infusion of other drugs
- Drug abuse/addiction: A personal history of drug abuse or addiction may be considered a relative or absolute contraindication to opioid therapy. However, clinicians program the pump and refill the reservoir, so the patient does not have access to the drugs (although at least one case report of patient gaining access to the hydromorphone in his implanted pump has been published).(40)
- Active infection: A general contraindication to surgery
- Anticoagulation: Surgical implantation in fully anticoagulated patients requires particular care(41)
- Inability to undergo general anesthesia: General anesthesia is typically administered for the pump implantation surgery
- Life expectancy of less than three(42) to six months(38)
- Body size insufficient to support weight and bulk of the device(42)
- For intraspinal administration:
    - Occluded spinal canal: The success of spinal infusion therapy depends on the ability of the infused drug to reach its site of action. For this reason, occlusion of the spinal canal has been listed as a contraindication.(39) However, the effect of a partially blocked spinal canal on pain control from spinal infusion has not been determined. Lack of efficacy of infusion therapy due to spinal occlusion may be detected during the test infusion before initiation of therapy.
    - Spinal infection or spinal instability: Contraindications to placing the catheter include spinal infection and spinal column instability.(43)

Clinical Practice Guidelines

Our searches of the National Guideline Clearinghouse™ (NGC) (www.ngc.gov) yielded three relevant clinical practice guidelines, one each from the American Society of Interventional Pain Physicians, the International Research Foundation for RSD (Reflex Sympathetic Dystrophy)/CPRS (Complex Regional Pain Syndrome), and independent authors, Sanders and colleagues, not writing on behalf of a professional organization. Sanders and his two coauthors all work in pain or physical rehabilitation centers, but their responsibilities there are not reported on the document we reviewed (two of the three authors have PhDs).

The American Society of Interventional Pain Physicians were supportive of the appropriate use of implantable infusion pumps for spinal pain.(44) Sanders and colleagues did not find that implantable infusion pumps met their criteria for "adequate evidence" for the treatment of Chronic Pain Syndrome, typified by pain lasting longer than the normal duration that causes functional impairment and is unresponsive to treatment. The International Research Foundation for RSD/CPRS neither recommended for nor recommended against the use of implantable infusion pumps. They did state that "morphine pumps" have not been clinically shown to be superior to oral morphine. This statement does not address the fact that patients are only considered candidates for implantable infusion pumps once all conservative treatments (e.g., oral morphine) have failed. These guidelines are summarized in Table 4, below.

Table 4. Clinical Practice Guidelines

Citation	Year	Chronic Pain Condition	Source of Information	Conclusion
Boswell et al., for the American Society of Interventional Pain Physicians(44)	2007	Spinal Pain	Systematic reviews and clinical studies, with emphasis on systematic reviews	"The evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignant or neuropathic pain. The evidence is moderate for long-term management of chronic pain."
Sanders et al., published by Siskin Hospital for Physical Rehabilitation(45)	2005	Chronic Pain Syndrome (CPS), which includes long-term/recurrent pain lasting longer than is typical and responds inadequately to treatment and impairs function	Literature overview with emphasis on clinical studies	"Studies and systematic reviews regarding the efficacy of infusion pumps and spinal cord stimulators have increased. Thus far, they have not met the current criteria for adequate supportive evidence to recommend application to CPS [chronic pain syndrome] patients." "Adequate evidence" was defined as two or more well-designed[1] prospective, controlled outcome studies that demonstrated effectiveness in at least 200 chronic pain patients
Kirkpatrick Ed., International Research Foundation for RSD/CRPS(46)	2003	Reflex sympathetic dystrophy (RSD)/Complex regional Pain Syndrome	Not reported	No conclusion offered, however, authors note that "morphine pumps" have not been clinically shown to be superior to oral morphine.

[1] Criteria for "well-designed" not specified

Manufacturers and Regulatory Status

Our searches of the Food and Drug Administration (FDA) Web site identified four original premarket approvals (PMA) for implantable infusion pumps. (Table 5: most recent documents appear first). Links to the FDA Web site are provided, as well as links to supplementary information on manufacturers' Web sites.

Medtronic currently markets two variants of programmable pumps and one nonprogrammable pump, and Codman currently markets three nonprogrammable pumps. The main difference between these pumps is that the Codman 3000 series and the Medtronic IsoMed are nonprogrammable and deliver medication at a constant rate only, whereas the SynchroMed is programmable to administer drugs in different doses and at varying time intervals. The primary difference among the Codman pumps is drug reservoir capacity and overall device size. The Medtronic programmable pumps also differ in size and reservoir capacity, and have some additional differences including alarm types, treatment information management features, and instructions for implantation.

Table 5. FDA Premarket Approvals (PMA) for Implantable Infusion Pumps

Trade Name	Applicant	PMA Number	Decision Date	Number of Supplements	Link to FDA PMA Page	Link to Manufacturer's Web site
Medtronic Isomed Infusion System	Medtronic Neuro-modulation	P990034	7/21/2000	84	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=9655	http://wwwp.medtronic.com/Newsroom/LinkedItemDetails.do?itemId=1101853461258&itemType=fact_sheet&lang=en_US
Constant Flow Implantable Pump with Bolus Safety Valve	Codman	P890055	03/11/1996	26	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=4921	http://www.codman.com/PDFs/3000%20pump.pdf
Medtronic Synchromed Pump & Infusion System	Medtronic Neuro-modulation	P860004	03/14/1988	23	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=9644	http://www.medtronic.com/neuro/paintherapies/pain_treatment_ladder/drug_infusion/pumps_pump_sel/drug_pumps_prog_pumps.html
Infusaid Implantable Infusion Pump Model – 100,200,4	Codman & Shurtleff, Inc.	P8000036	03/03/1982	84	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=4922	No information on Codman Web site

Currently, only two drugs, morphine and ziconotide, are approved by the FDA for use with an implantable infusion pump for CNCP. However, some physicians prescribe the drugs they believe are most appropriate off-label, such as when patients have allergies or sensitivities or insufficient pain relief with morphine sulfate. Ziconotide is intended for patients who have not had sufficient pain treatment success with other infused drugs.

FDA Warning Letters

The FDA had issued two warning letters to Medtronic regarding their devices.

The first letter was issued on August 29, 2006, regarding an inspection of their Minneapolis plant that revealed lack of conformity with Current Good Manufacturing Practice (CGMP) requirements, in which eight "significant deviations" were cited. Four of the grievances pertained to the catheter tip bond design and manufacturing process, and four pertained to failure to identify, correct, or prevent other nonconforming product quality problems including tip detachments, pump motor stalls, and traceability cards.(47)

The second letter was issued on July 3, 2007. This letter reports that FDA inspection found that Medtronic devices are misbranded because material or information pertinent to adverse events for serious injury associated with their product were not reported to the FDA. Many of these adverse events involved granuloma or inflammatory mass at or near the distal tip of the intrathecal catheter used with their implantable infusion pump.(48) No Medtronic, Inc. response to either of these letters is posted on the FDA Web site.

FDA Recall

The FDA issued a Class I Recall on January 21, 2008, regarding Medtronic implantable infusion pumps. Class I recalls are for "dangerous or defective products that predictably could cause serious health problems or death."(49) This recall did not require any action on the part of patients or physicians, according to Medronic.(50) This recall pertains to a number of models of the SynchroMed EL, Synchromed II, and Isomed pumps (all models listed in FDA letter, link provided in *References* list). The reason for the recall was a labeling update including updated patient management and treatment recommendations, and because of adverse event reports of inflammatory mass formations at or near the distal catheter tips when opioids, baclofen, or chemotherapeutics are administered.(51) That same month, Medtronic issued a letter to healthcare professionals in response to the FDA recall(50); the Medtronic letter was detailed in the *Adverse Events* section.

Payer Status

Centers for Medicare & Medicaid Services (CMS)

CMS issued a national coverage decision for infusion pumps (manual section 280.14) in February 1994 as durable medical equipment. The latest version of the policy was implemented December 17, 2004, and made effective February 18, 2005, This determination includes implantable infusion pumps for epidural or intrathecal administration of opioid drugs for CNCP. Other drugs may be covered if the drug is verified as "reasonable and necessary for the treatment of an individual patient," and must be administered by an implanted infusion pump. Under this policy, pump recipients must satisfy the following criteria:

- Life expectancy of at least three months
- Unresponsive to less invasive medical therapy, such as systemic opioids and attempts to correct underlying physical and psychological abnormalities
- Successful intraspinal opioid trial, defined by acceptable pain relief and side effects and their impact on daily living, and patient acceptance

Commercial Payers

We searched nine commercial payers' Web sites to identify relevant reimbursement policies. Four of the payers did not have any relevant policy (Wellmark, Medica, BCBS of Alabama, BCBS of Massachusetts), and a fifth did not have a policy specific to CNCP (HealthPartners). The four other payers all cover the use of implantable infusion pumps for CNCP provided that certain criteria are satisfied (Regence, Humana, CIGNA, and Aetna. See Table 6, below). These criteria are consistent with indications for receiving implantable infusion pumps according to FDA labeling, such as: chronic pain that is insufficiently responsive to other treatments, an infusion trial is successful, a psychological examination that rules out psychological causes or contributions to the pain or that suggests the patient may not respond well to the treatment, life expectancy is at least three months. Only one payer, Aetna, stipulates that the pump should be used only with FDA-approved medications.

Table 6. Commercial Payer Policies

Payer and Link to Policy	Relevant Policy	Policy Number	Date Effective
Regence http://blue.regence.com/trgmedpol/surgery/sur18.html	Severe, chronic, intractable pain (intravenous, intrathecal, or epidural infusion of Duramorph, Dilaudid and Clonidine) of malignant or non-malignant origin in patients who have a life expectancy of at least 3 months and who have proven unresponsive to less invasive medical therapy as determined by the following: a. The clinical history suggests the patient would not respond adequately to non-invasive pain control methods (such as systemic opioids) and b. A preliminary trial of opioids with a temporary intrathecal/epidural/intravenous catheter must be undertaken to substantiate acceptable pain relief, degree of side effects, and patient acceptance.* * An adequate preliminary trial varies from patient to patient. For example, a cancer patient might be considered for a short trial, perhaps even a single injection, whereas a patient in whom improved function is a major goal of therapy might warrant a prolonged trial with objective assessment.	18	4/05/05; Not scheduled for further review
Humana http://apps.humana.com/tad/tad_new/returnContent.asp?mime=application/pdf&id=5576&issue=827	"A temporary trial **MAY*** be covered for spinal (intrathecal or epidural) opioid drugs (e.g., morphine) for the treatment of severe chronic intractable pain due to malignant or non-malignant origin when **ALL** of the following criteria are met: Life expectancy of at least 3 months; **AND** The patient's history must indicate that he/she did not respond adequately to noninvasive methods of pain control, such as systemic opioids (including attempts to eliminate physical and behavioral abnormalities which may cause an exaggerated reaction to pain.) A temporary trial for **non-malignant** intractable pain requires that a psychological evaluation has been obtained and indicates that the member is a favorable candidate for permanent intrathecal pump implantation. Permanent implantation of an intrathecal (intraspinal) infusion pump for the administration of opioid medications to treat chronic intractable pain **MAY** be covered with a temporary trial that has been successful. Successful is defined as: A temporary trial of spinal opioid drug administration must have been undertaken with **ALL** the criteria listed above met; **AND** The temporary trial has been successful and substantiates an acceptable degree of pain relief and side effects (including activities of daily living) with patient approval."	CPD-0307-000	3/27/07

Payer and Link to Policy	Relevant Policy	Policy Number	Date Effective
CIGNA http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0370_coveragepositioncriteria_implantable_infusion_pumps.pdf	**"CIGNA* HealthCare covers the use of an implantable infusion pump as medically necessary when used to administer opioid drugs (e.g., morphine) or nonopioid analgesics intrathecally or epidurally for the treatment of severe, chronic intractable pain conditions when ALL of the following criteria are met:** • The patient has experienced failure of, or has intolerance or contraindications to, noninvasive methods of pain control, including systemic opioids. • Attempts have been made to eliminate physical and behavioral health abnormalities that may contribute to an exaggerated sensation of pain. • A preliminary trial of intraspinal opioid drug administration has been undertaken with temporary intrathecal/epidural catheter to substantiate pain relief, side effects and patient acceptance."	0370	6/15/2007
Aetna http://www.aetna.com/cpb/medical/data/100_199/0161.html	Aetna considers implanted infusion pumps medically necessary durable medical equipment (DME) when all of the following criteria are met: • The drug is medically necessary for the treatment of members (see medical necessity criteria for various types of infusion pumps below); *and* • It is medically necessary that the drug be administered by an implanted infusion pump; *and* • The infusion pump has been approved by the FDA for infusion of the particular drug that is to be administered. *Opioid drugs for treatment of chronic intractable pain* An implantable infusion pump is considered medically necessary when used to administer opioid drugs (e.g., morphine) and/or clonidine intrathecally or epidurally for treatment of severe chronic intractable pain in persons who have proven unresponsive to less invasive medical therapy as determined by the following criteria: 1. The member's history must indicate that he or she has not responded adequately to non-invasive methods of pain control, such as systemic opioids (including attempts to eliminate physical and behavioral abnormalities which may cause an exaggerated reaction to pain); *and* 2. A preliminary trial of intraspinal opioid drug administration must be undertaken with a temporary intrathecal/epidural catheter to substantiate adequately acceptable pain relief, the degree of side effects (including effects on the activities of daily living), and acceptance.	0161	Not reported

* All emphases in this table reproduced as written in payer decision reports.

Reimbursement Coding

Examples of common International Classification of Diseases (ICD)-9 codes for infusion systems for CNCP reported by Medtonic in 2004(52) are listed in Table 7, below.

Table 7. Examples of Commonly Billed ICD-9 Codes

Reason for Billing	Code
Diagnosis Codes	
Arachnoiditis, chronic or due to prior procedure	322.9
Reflex sympathetic dystrophy (RSD) of the lower limb, also known as complex regional pain syndrome	337.22
Phantom limb pain, syndrome	353.6
Causalgia of the lower limb	355.17
Peripheral neuropathy of the lower limb	355.8
Post-laminectomy syndrome, lumbar region	722.83
Radicular syndrome, lower limb	724.4
Osteoporosis	733.0X
Procedure Codes	
Insertion of catheter into spinal canal for infusion of therapeutic or palliative substances	03.90
Injection of other agent into spinal canal	3.92
Insertion of totally implantable infusion pump	86.06

Descriptions of Healthcare Common Procedure Coding System (HCPCS) codes used for infusion systems reported by Medtronic in 2004(52) include:

- Infusion pump system, implantable, non-programmable (includes all components)
- Infusion pump system, implantable, programmable (includes all components)
- Implantable intraspinal (epidural/Intrathecal) catheter used with implantable infusion pump, replacement
- Implantable programmable infusion pump, replacement (excludes implantable intraspinal catheter)
- Injection, morphine sulfate (preservative-free sterile solution), per 10 mg
- Refill kit for implantable infusion pump

Methods

Key Questions and Outcomes of Interest

To evaluate the efficacy and safety, and to profile the cost and cost-effectiveness of implantable infusion pumps for CNCP, we addressed the following Key Questions:

1. What is the evidence for efficacy and effectiveness of implantable infusion pumps?
2. What is the safety profile of implanted infusion pumps?
3. Is there any evidence of differential efficacy or safety issues amongst special populations?
4. What are the cost implications and cost effectiveness for implantable infusion pumps?

The analytic framework in Figure 3 shows the relationship between the patient population, the intervention, and outcomes. Key Questions 1 and 2 are represented by number in this framework. For Key Question 3, we considered all outcomes for Key Questions 1 and 2 for any special population subgroups reported in the literature or identified using statistical techniques in Key Questions 1 and 2. Key Questions 3 and 4 are not represented in the figure.

We sought data on a variety of outcomes to address the efficacy and effectiveness of implantable infusion pumps in Key Question 1. Measures of efficacy and effectiveness included pain and pain relief, trial discontinuation from clinical study due to insufficient pain relief, quality of life, functional status , employment status, other medications and therapies used, and change in quantity of infused dose required over time.

Although pain is the primary outcome, we also evaluated additional outcomes besides pain because chronic pain patients typically experience a number of other pain-related problems, including decreased functional status and quality of life, inability to work, and excessive use of medication.(53) Any assessment of the treatment of chronic pain must therefore address these problems as well. Tools used to measure efficacy and effectiveness are presented in the following paragraphs.

Pain: The most commonly used scales are visual analogue scales (VAS) and numerical rating scales (NRS). In VAS, patients indicate how much pain they have by selecting a point on a line, with one end of the line representing no pain and the other end of the line representing the worst pain imaginable. For NRS, patients indicate how much pain they have verbally, with zero representing no pain and the upper limit of the scale (typically 10 or 100) representing worst pain possible. In studies where more than one pain scale was reported, we extracted data on VAS or NRS preferentially to maximize comparability across studies analyzed. On a scale of 0-10, VAS and NRS scores can be categorized by level of severity as follows:(54)

1-4: Mild Pain

5-6: Moderate Pain

7-10: Severe Pain

Quality of Life: Quality of life is a particularly meaningful outcome for long-term therapy because it reflects both the benefits (e.g., pain relief) and harms (e.g., side effects) of treatment. Three different scales that measure quality of life were used by the studies included in the evidence base of this report. The Tollison Quality of Life Scale is an 18-item scale for which scores of 18 to 108 are possible. Higher scores indicate lower quality of life.(55) The Questionnaire of the European Foundation of Osteoporosis (QUALEFFO) assesses domains including pain, physical functional status, social functional status, general health perception and mental functional status. For more information regarding the QUALEFFO and its validation, refer to Lips et al. 1999.(56) Higher scores represent lower quality of life. The standard form with 36 questions (SF-36) is very commonly used in medical research. Higher scores on the scale of

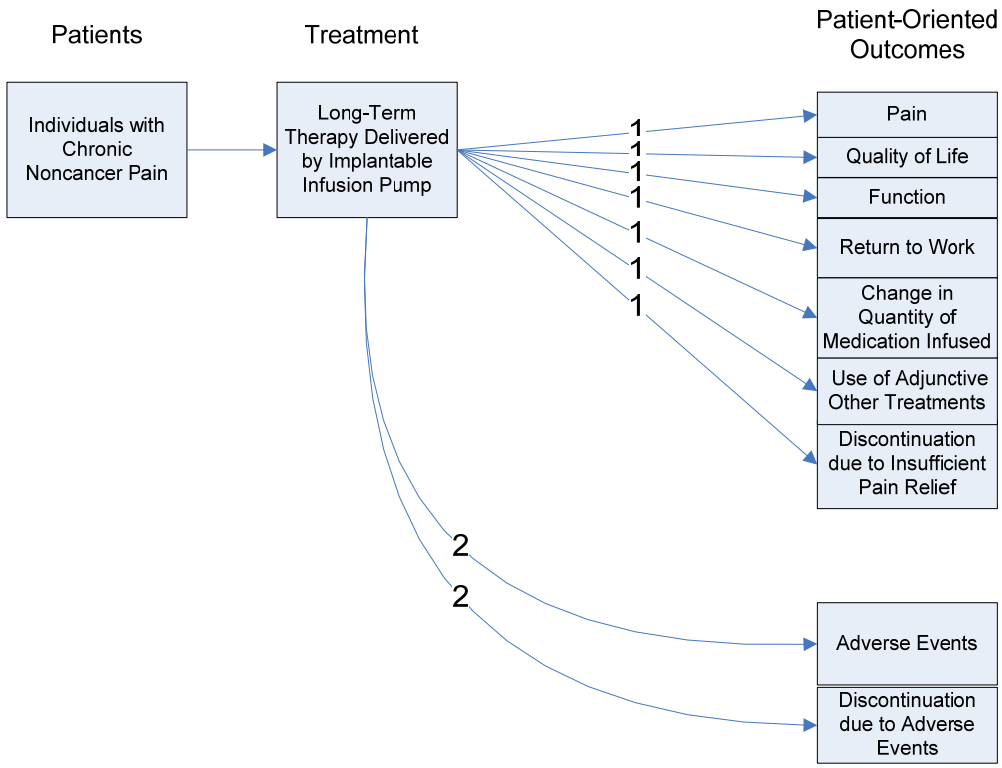
0 to 100 represent better quality of life. For more information on this instrument and to see samples of the scales, visit http://www.sf-36.org.

Functional status: Functional status associated with use of implantable infusion pumps was measured by three different scales. One is the chronic illness problem inventory (CIPI), a 65-item questionnaire that measures the impact of chronic illness on several different quality-of-life dimensions, including sleep and marital difficulty. Higher scores indicate lower quality of life. For more information, refer to a validation study on this scale.(57) The third is the short-form Sickness Impact Profile (s-SIP). For more information on the SIP, refer to Deyo 1986(58) On the s-SIP, lower scores indicate improvement. One study reported function in terms of the Oswestry Disability Index (ODI). The ODI is specific to back pain, and scores are reported from 0% to 100%, with 0% indicating no disability and 100% indicating complete disability.

To assess the acceptability of implanted infusion pump treatment, we analyzed rates of discontinuation from clinical study due to insufficient pain relief (Key Question 1) and discontinuation from clinical study due to adverse events (Key Question 2). These rates estimate the proportion of patients who prefer not to continue therapy within the context of the clinical study because of inadequate pain relief or intolerable adverse events that outweigh any pain relief benefit. This outcome measures the proportion of patients who chose to end their participation in the clinical study; however, these patients do not necessarily discontinue therapy using their implanted infusion pump altogether.(59)

To address the safety of this treatment, we cataloged and reported on adverse events from case series and MAUDE (Key Question 2). All reported adverse effects and events in included literature and MAUDE were included. We also analyzed rates of discontinuation from clinical study due to adverse events, as described above.

Figure 3. Analytic Framework



Literature Search Strategy

The clinical studies included in this technology assessment were identified using a multi-staged study selection process, and selection was based on inclusion criteria that were determined *a priori*. Use of *a priori* inclusion criteria reduces the risk of bias because the decision to include or exclude each study is independent of the results of the study. In the first stage of the selection process, we performed a comprehensive literature search using broad criteria. In the second stage, we retrieved all articles that appeared to meet the *a priori* inclusion criteria based on their published abstracts. In the final stage of the study selection, we reviewed full text of each retrieved article, assessed its internal validity (sometimes referred to as quality), and verified whether it met the *a priori* inclusion criteria.

Eleven databases were searched, including EMBASE and PubMed (1990 through April 15, 2008) and all Cochrane databases and registries (1990 through Issue 2, 2008). We used search terms including the following: chronic pain (pain, intractable[major heading (mh)] OR (pain AND (chronic OR intractable OR refractory OR persistent OR chronic disease[mh]), a list of painful conditions, and all medications in current use with implantable infusion pumps by generic and proprietary names. Full search strategies are shown in Appendix A. We also examined reference lists from identified studies and reviewed gray literature (reports and studies produced by local government agencies, private organizations, educational facilities, and corporations that do not appear in the peer-reviewed literature) for additional studies not identified by other means.

Study Selection Criteria

Use of explicit inclusion criteria, decided upon before data have been extracted, is a vital tool in preventing reviewer biases. Some of these *a priori* criteria are based on study design, and other criteria ensure that the evidence is not derived from unusual patients or interventions and/or outmoded technologies.

In addition to data from controlled trials, we sought studies that reported data from long-term uncontrolled case series. Although open-label uncontrolled time-series studies may be more susceptible to bias than controlled studies, we chose to analyze data from these studies in the absence of a sufficient quantity of controlled trial because case series then provide the best available evidence.

The study inclusion criteria were as follows:

- *Study was reported in the English-language literature.*

  Studies have not consistently shown that including non-English studies substantially affects the analysis outcomes.(60-63)

- *Study was reported as a full-length article rather than as an abstract or letter.*

  Published abstracts and letters do not include sufficient details about experimental methods to permit verification and evaluation of study design. However, we would include data from any abstract that reported additional outcomes from a study and patient group that had been reported in a full-length article that met all inclusion criteria.

- *Clinical studies may be of either a prospective or retrospective design. However, retrospective studies must assess a consecutive series of patients or randomly-selected patients.*

  Retrospective studies may be more susceptible to bias than prospective studies, because selecting a patient population based on their outcomes is possible. Retrospective study designs may therefore threaten internal validity and may impart bias. To minimize these threats, we require that patients must be selected randomly or as a consecutive series. This protects against the retrospective selection of patients due to certain characteristics (e.g., treatment response) that would compromise the internal and external validity of any study.

For adverse events, we will also consider retrospective data from MAUDE.

- *Study reported at least one of the outcomes of interest.*

  The outcomes of interest are listed in the key questions; other outcomes are beyond the scope of this report.

- *Study reported data for at least 10 patients treated with an implantable infusion device.*

  Patients described in case reports and small case series, as well as the treatments employed in small studies, may be unusual. Furthermore, such data may only represent a center's initial experience with a technology and may therefore misrepresent the effectiveness of a technology.

- *Study did not contribute data for patients who also contributed identical data to other included studies.*

  Double-counting of patients must be avoided, because it inflates and may bias the evidence base. Determinations of overlap between studies were based on comparative examinations of study enrollment dates, patient characteristics, treatment regimens, author names, and author affiliations. If the same study had been published more than once, we used the data from the publication with the most complete information.

- *Study data on enrolled only patients who had CNCP according to the International Association for the Study of Pain (IASP) definition (pain lasting at least three months).*

- *Outcomes requiring patients to remember their previous health (e.g., pain, quality of life, or disability) were excluded because such outcomes are too susceptible to bias.*

- *For efficacy outcomes (pain, quality of life, and functional status), patients were treated for at least six months.*

  For this report, we defined "long term" treatment as treatment lasting six months or longer, which may be necessary for some patients with chronic pain.

  Harms outcomes from clinical studies will be collected from long-term studies in which patients were enrolled with the intention of receiving treatment for at least six months. Adverse events experienced at any time point during these long-term studies will be reported.

- *On average, patients must have reported at least moderate to severe CNCP before undergoing pump implantation.*

  Implanted pumps are only indicated for moderate to severe pain. Standard tests may be used to establish the baseline pain level of patients. A numerical rating score (NRS) or visual analog score (VAS) of at least 5/10 or 50/100, or on other scales, a score indicating moderate pain is the minimum pain level to satisfy this criterion.

- *Studies measured pain, quality of life, and functional status with an instrument for which the properties of reliability and validity have been reported in published literature.*

- *For the questions on efficacy, effectiveness and harms (Key Questions 1, 2, and 3), if a study reports an outcome of interest and meets the other outlined inclusion criteria, it will be included regardless of whether it was randomized or had a control group.*

- *For the cost question (Question 3), we will include any original published cost analysis or cost-effectiveness analysis of implantable infusion pumps when used for the long-term treatment of chronic, noncancer pain and exclude other primary diagnoses such as spasticity.*

Evaluation of Strength and Stability of Evidence

To evaluate the stability and strength of a body of literature, we use the ECRI Institute strength- and stability-of-evidence system. This system, which is described in Treadwell et al. (2006),(64) employs decision points that collectively yield overall categories. The decision points in the system address five general aspects of the evidence: internal validity, quantity, consistency, robustness, and magnitude of effect (see Appendix B). Internal validity refers to the degree of potential bias in the design or conduct of studies. Quantity refers to the number of studies and the number of enrolled patients. Consistency addresses the degree of agreement among the results of available studies. Robustness is the insensitivity of conclusions to minor alterations in the data. Magnitude of effect concerns the quantitative amount of benefit (or harm) that patients experience after treatment. These evidential aspects are described in greater detail in Appendix B.

Categorization of the evidence is based on the strength of the evidence for a qualitative conclusion and stability of a quantitative estimate as strong, moderate, weak, or inconclusive. The qualitative conclusion addresses the question "Does it work?" The quantitative estimate addresses the question "How well does it work?" This distinction allows an evidence base to be considered unstable in terms of the quantitative estimate of effect (e.g., if estimates vary widely among studies). However, this distinction also allows it to be considered strong or moderate with respect to the qualitative conclusion (e.g., if all studies nevertheless demonstrate the same direction of effect). In evidence bases comprised of case series, we do not form qualitative conclusions or rate the strength of evidence for outcomes without comparisons (e.g., proportion of patients with 50% of pain relief, discontinuation from clinical study due to adverse events).

Where possible, we used meta-analysis to investigate the outcomes because meta-analysis provides a formal framework for investigating heterogeneity (e.g., finding out why outcomes differ among different studies) and enable rigorous sensitivity analyses (tests that evaluate the stability of conclusions). For some outcomes, we arrive at a conclusion that is qualitatively inconclusive and/or quantitatively unstable. In these instances, we do not form any conclusions regarding the strength or stability of the findings. Rather, we note that the findings are unstable and/or inconclusive and do not draw conclusions regarding the findings. However, we do present the findings so that decision makers may consider what evidence is available. Interpretations of these terms (strong, moderate, weak/low, and inconclusive/unstable) appear in Table 8.

Table 8. Interpretation of Strength- and Stability-of-Evidence Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion (Direction of Effect)	
Strong Evidence	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate Evidence	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature at this time.
Weak Evidence	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Inconclusive Evidence	Although some evidence exists, it is not of sufficient strength to warrant drawing an evidence-based conclusion from it. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Quantitative Conclusion (Magnitude of Effect)	
High Stability	The estimate of treatment effect included in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate Stability	The estimate of treatment effect included in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature at this time.
Low Stability	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

Methods of Analysis

In any systematic review, reviewers must decide how to summarize evidence from multiple studies. If case series satisfy our criteria and provide acceptable evidence, we do sometimes perform a meta-analysis using them. The meta-analysis of case series can follow logically from a) the consideration of case series based on sensitivity to patients' histories and possible futures and b) the aggregation of results using standardized meta-analytic techniques. Although there was variation across studies with respect to characteristics of enrolled patients and treatment protocols, all included studies addressed the use of implantable infusion pumps for CNCP. Therefore, provided all other criteria for meta-analysis were satisfied, we used meta-analysis to analyze the data for each outcome. Meta-analysis is known to reduce the risk of random error to produce a more reliable and precise effect estimate, and to potentially produce more generalizable results because the results from a variety of clinical contexts and settings are averaged. However, we did not necessarily use meta-analysis to arrive at a single point estimate for an effect size: In many cases we refrained from such an estimate. There are other reasons for utilizing meta-analytic techniques. These reasons for using meta-analysis apply regardless of whether the studies were all randomized and blinded studies, or a mix of blinded and unblinded studies, or a mix of randomized and non-randomized studies, or consisted solely of case series (as in this review).

- Increasing the power of an evidence base to determine the general direction of effect (i.e., an increase or decrease in pain), especially when an evidence base is comprised of many small studies that, considered in isolation, could lead to a Type II error (concluding there is no effect when there really is one).

- Reducing the risk of random error and production of a more reliable and precise effect estimate.(3)

- Transparent methodology for drawing conclusions, or for deeming the findings too inconclusive or unstable to enable conclusions, thereby limiting the influence of subjective judgment on data aggregation.

- Provision of formal, objective framework that can be used to investigate potential reasons for different findings across studies. Using the meta-analytic techniques of meta-regression and subgroup meta-analysis, one can investigate whether differences in outcomes are potentially associated with differences in study protocols (e.g., drug administered, duration of treatment) or characteristics or patients enrolled (e.g., most common painful condition). This could potentially enable identification of study protocols associated with better or worse outcomes and patient groups who are most or least likely to benefit from therapy with an implantable infusion pump.

- Formal, objective methods to evaluate the consistency and robustness of conclusions.

- Avoiding the pitfalls of narrative systematic reviews, such as vote count methods in which the qualitative findings of each study in the evidence base is considered side-by-side but never pooled quantitatively or considered with respect to the sample size (i.e., precision) of each study, possibly leading to erroneous results, and subjectivity in assessing relationships between outcomes and potential moderator variables, especially as the number of studies increases.(2,3) Vote counting has been recommended as a method of "last resort," only to be performed when effect sizes and significance levels of the studies are unavailable.(3)

- May produce more generalizable results because the results from a variety of clinical contexts and settings are averaged.(3)

A potential risk of meta-analysis occurs when summary findings are used to draw conclusions without critically evaluating the evidence base. To avert this risk, ECRI Institute uses a system of *a priori* systematic protocols to evaluate the evidence base for each outcome in a transparent and reproducible manner that only allows for conclusions to be drawn when the evidence base has satisfied rigorous criteria. Our protocols and the specific risks they are intended to minimize are summarized in Table 9, below, and are fully explained in Appendix B.

Table 9. The ECRI Institute System's Quality Control Measures for Drawing Conclusions

Threat to Validity of Conclusion	ECRI Institute Protocol	ECRI Institute Quality Control Measure (and decision point with full details, shown in Appendix B)
Unacceptably low internal validity (e.g., quality)	All studies meeting other inclusion criteria are evaluated using internal validity scales selected with respect to study design type	Exclude studies with unacceptably low quality scores from evidence base. (See Decision Points 1 and 2)
Too few studies	The number of studies reporting an outcome is considered before performing meta-analysis or attempting to draw a conclusion	If fewer than three studies address an outcome in a statistically compatible manner, no quantitative conclusion is drawn. (See Decision Point 3) If only two studies are identified and they are qualitatively consistent, a qualitative conclusion may be possible. (See Decision Points 8 and 9)
Lack of unresolved consistency among studies (i.e., substantial heterogeneity)	Evaluate evidence base (all studies being considered for a given meta-analysis) for consistency using meta-analytic statistics. When inconsistency is detected, attempt to resolve it using statistical techniques if possible.	Evidence bases with unresolved inconsistencies are considered unstable. No quantitative conclusion is drawn from them.(See Decision Point 4) We may present the meta-analytic findings for the consideration of decision-makers, but we do not draw evidence-based conclusions regarding them. (See Table 8 for full interpretation of "unstable" quantitative estimates) Qualitative conclusions may still be possible. (See Decision Points 8 and 9)
Lack of robustness in summary statistic	Evaluate evidence base for robustness using meta-analytic statistics.	When lack of robustness is detected, the strength of evidence for the qualitative conclusion is downgraded, or, no qualitative conclusion is drawn at all, in which case the evidence base is considered inconclusive. (See Decision Point 5 for full details and Table 8 for full interpretation of "inconclusive" qualitative estimates)

Follow-up times in included studies ranged from six months to over four years. We did not pool data for specific time points because there were generally too few studies reporting data at any given specific time point, and reporting outcomes for a different subset of studies at each time point would confound the relationship between differences among studies and duration of treatment. For these reasons, we used the last reported time point (or average time point) of each study and then performed meta-regression to assess whether the treatment duration was associated with the outcomes.

The choice of effect-size metric depended on whether reported outcome data were continuous or dichotomous. Pre-post treatment differences in outcomes measured using continuous data (e.g., visual analogue pain scales, quality-of-life scales) were standardized into a common metric, the standardized mean difference (SMD), also known as Hedges' d.[2] A correlation coefficient of 0.50 was used, since pre-post data are not independent.(72) For continuous pain scores, we converted summary SMD and 95% CIs to pain scores on a scale of 0-10 . Note that the scores attained using this method were calculated using a correlation coefficient. We also present what the mean follow-up score is when no correlation coefficient

[2] Standardized mean difference (SMD) / Hedge's d: $d = (\mu_t - \mu_c)/s^*$, where μ_t is the sample mean of the treatment arm, μ_c is the sample mean of the control arm, and s^* is the pooled standard deviation.(3) For use with case series, data from two time points, before and after treatment, are used instead of data from two groups.

is used. To assess pre-post employment rates, we used an odds ratio with a correlation coefficient of 0.5. For dichotomous data (e.g., proportion of patients with clinically important pain relief), we used the logit transformation of the proportion of patients for which a given outcome was reported as the effect size metric, and for ease of interpretation we present raw proportions.

In our assessment of the meaning of continuous pain scores, we define the long-term minimally clinically significant change in pain scores (smallest amount of pain relief that is meaningful) as a change of 2 on a scale of 0-10 (note: this is 20 percentage *points,* not to be confused with 20%). Methodological studies have found that this quantity of pain relief is clinically important in general pain trials(54)and for individuals with chronic musculoskeletal pain(73) and chronic low back pain(74), which are the most commonly causes of pain of patients seeking treatment in the case series evaluated in the *Synthesis* section.

For the assessment of proportions of patients attaining clinically important pain relief, we used thresholds of 25% and 50% pain relief. We used the minimum reduction of 25% pain relief long-term as clinically meaningful because this number has been identified as clinically meaningful by researchers studying the use of implantable infusion pumps for patients with CNCP in light of the challenges of treating a patient population refractory to other available therapies, and patient preferences:

- "The rationale for using a 25% improvement was based on our clinical observation that most patients with chronic pain for whom all, reasonable, more conservative treatments have failed are satisfied with the therapy and think the expense and risks are justified if they receive long-term relief of at least 25% of their pain."(6)

- "Long-term success was defined as 25% or greater decrease in VAS pain intensity. In this study, we have selected a lower threshold for defining success as compared to other pain relief modalities, where the convention has been to use a 50% reduction as a threshold because this patient group has been more refractory to various pain relief therapies. They have been on long-term narcotic therapy and are quite happy and satisfied with a long-term 25% pain relief."(68)

We first tested the available data to determine whether the results of the studies included in the meta-analysis differed from one another by more than expected by chance (i.e., heterogeneity testing). We defined substantial heterogeneity as $I^2 \geq 50\%$(75,76) If the data were consistent (not substantially heterogenous), then we pooled the study results in a DerSimonian and Laird random-effects model to obtain a summary estimate and its confidence interval. If the results did differ (i.e., if the data were heterogeneous) and the evidence base for the outcome contained five or more studies, we performed random-effects meta-regression in an attempt to explain the heterogeneity (using the permutation test *P*-value as described by Higgins and Thompson).(77) Evidence bases with unresolved heterogeneity have a potential lack of reliability. In these cases we report the meta-analytic findings but emphasize that the 95% confidence intervals provide a reasonable range of where the effect size(s) lie. These approaches are described in more detail in Appendix B.

Sensitivity analyses were performed using cumulative random-effects meta-analyses (for which studies were added to the analysis one at a time in order of publication date) and impact meta-analyses (in which we removed and replaced each study one at a time) to test the robustness of our findings.(78-80) For continuous outcomes, assumptions about correlation coefficients were tested by sensitivity analyses in which we varied the correlation coefficient from 0.01 to 0.99 to determine whether the summary effect size was stable.(81) We considered more than a 25 percentage point change in summary effect size upon manipulation of the correlation coefficient to indicate that the quantitative estimate of the meta-analysis is not stable.

Infusion trials evaluate pump candidates who meet all other criteria for sufficient response to infusion therapy (typically at least 50% pain relief) without intolerable adverse events. Only the candidates with successful infusion trials receive an implantable infusion pump. This trial process is intended to identify the patients who will benefit most from therapy and be least likely to discontinue therapy due to insufficient pain relief or intolerable adverse events. For the outcomes discontinuation from clinical study due to insufficient pain relief and discontinuation from clinical study due to adverse events, we meta-analyzed rates of discontinuation from clinical study for all studies that reported this outcome, and also for the subset of studies that used infusion trials to select pump recipients, and the subset that did not use an infusion trial on all pump candidates to select pump recipients.

Comprehensive Meta-Analysis (Biostat, Englewood, NJ) software was used for most statistical analyses. Meta-regression with permutation tests was performed using STATA (StataCorp LP, Bryan/ College Station, TX) software.

Included Studies and Publications

For this report we first searched for randomized controlled trials (RCTs) or other controlled trials on the long-term harms and efficacy of implantable infusion pumps. However, no well-controlled long-term trials exist, so we evaluated the best available evidence, case series. Case series are generally considered a lower level of evidence for measuring the impact of an intervention than controlled trials. The reason is typically that, without a control group, there is no empirical estimate of what the patients' outcomes would have been if they had *not* received the treatment of interest. Thus, one would ideally have a control group in every circumstance. This is absolutely essential when patient's future outcomes are highly uncertain. However, if the natural history of a disease is stable, substantive improvement would not be expected without the intervention in question. Case series may therefore still provide meaningful information regarding a technology, especially when the natural history of the disease is well-known, and no substantial placebo effect is anticipated. This is especially true if a decision regarding the technology must be made and there is either no time to wait for controlled trial results to become available, or no controlled trials are expected.

Chronic noncancer pain patients who are candidates for receiving pain medication delivered by implantable infusion pumps have a fairly stable natural history of disease, lasting as long as a decade on average in some of the case series we identified. In addition, their course of disease would not be expected to vary as dramatically as other pain patients' because pump candidates have exhausted all other available interventions for pain, including surgery where appropriate, and have not had substantial reductions in pain. These individuals are therefore resistant to not only pain-reducing treatments, but also substantial placebo effects. For these reasons, we determined that case series provide acceptable data in the absence of controlled trials. We used case series in this analysis under the assumption that patients' future outcomes would be similar to their baseline outcomes if no treatment is given.

Of 549 identified abstracts, we identified 88 as potentially relevant and retrieved them in full. In addition, we reviewed in full one cost analysis provided to us by the Washington State Health Technology Assessment Program. Of those, 72 items did not meet inclusion criteria. Reasons for exclusion of clinical studies include not having pain as a patient enrollment criterion or reporting that patients were in pain at baseline (26 studies), retrospective design and having the patient selection method not reported as consecutive or random (10 studies), not being a clinical study (7 studies), fewer than ten patients treated with intrathecal infusion pump (6 studies), for not treating patients for at least six months (6 studies), all or a substantial portion (>15%) of the patients enrolled had cancer-related pain (4 studies), for reporting duplicate data reported in an included study (1 study), and for lack of relevance (1 study). Reasons for exclusion of cost analyses include lack of relevance to implantable infusion pumps (4 publications), not being a cost analysis (1 publication), evaluation of short-term use of pumps only (1 publication), and analysis of substantial portion of patients with cancer (1 publication). Excluded studies are listed in Table 29 of Appendix A.

Thirteen case series and four costs analyses remained for inclusion. However, only 16 total publications were reviewed because one publication provided both a clinical study and a cost assessment. The process of identifying these studies is shown in Figure 4, below. These studies are listed and briefly described in Table 10. We present the analysis findings in *Results Synthesis*.

Figure 4. Study Inclusion Diagram

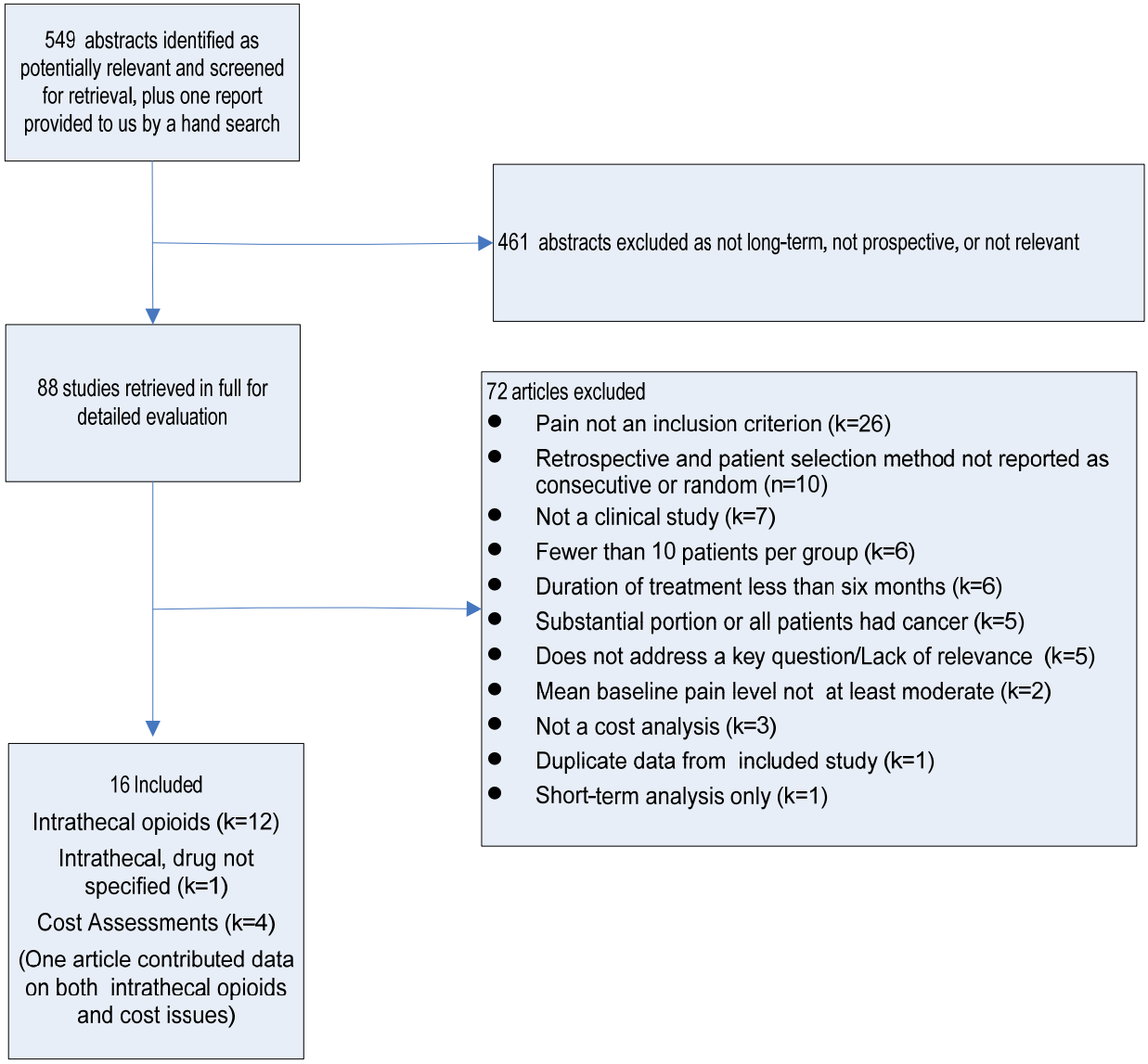


Table 10. Included Studies and Key Questions Addressed

Study	Year	Drug(s)	Pain Condition	Number implanted with infusion pump	Key Question (KQ) 1									KQ 2		KQ 3	KQ 4
					Pain			Discontinuation from Clinical Study due to Insufficient Pain Relief	Quality of Life	Functional status	Employment Status	Other Medications and Treatments	Dose of Infused Medication Over Time	Discontinuation from Clinical Study due to Adverse Events	Adverse Events	Use of Pumps in Different Populations	Cost Issues
					Continuous	≥25% Relief	≥50% Relief										
Krames and Lanning(65)	1993	Morphine equivalents with or without bupivacaine	Various causes	16	*								✓	✓	✓		
Kanoff(7)	1994	Morphine	Mixed	15	*						✓	✓		✓	✓		
Hassenbusch et al.(39)	1995	Morphine or sufentanil citrate	Neuropathic	18	✓	✓	✓	✓				✓	✓	✓	✓		
Tutak and Doleys(66)	1996	Morphine or fentanyl	Unspecified	26							✓		✓	✓	✓		
de Lissovoy et al.(9)	1997	Morphine	Failed back surgery syndrome (FBSS)	NA**													✓
Angel et al.(67)	1998	Morphine	FBSS	11	✓	✓	✓	✓				✓	✓	✓	✓		
Anderson and Burchiel(6)	1999	Morphine	Nociceptive and neuropathic, many with FBSS	30	*	✓	✓	✓		*	✓	✓	✓	✓	✓		
Kumar et al.(68)	2001	Morphine, with clonidine if needed	Various causes	16	✓	✓	✓	✓				✓	✓	✓	✓		
Mironer and Tollison(55)	2001	Methadone	FBSS	24	✓	✓	✓	✓	✓				✓	✓	✓		

					Key Question (KQ) 1									KQ 2		KQ 3	KQ 4
					Pain												
Study	Year	Drug(s)	Pain Condition	Number implanted with infusion pump	Continuous	≥25% Relief	≥50% Relief	Discontinuation from Clinical Study due to Insufficient Pain Relief	Quality of Life	Functional status	Employment Status	Other Medications and Treatments	Dose of Infused Medication Over Time	Discontinuation from Clinical Study due to Adverse Events	Adverse Events	Use of Pumps in Different Populations	Cost Issues
Rainov et al.(69)	2001	Morphine (with bupivacaine, clonidine, or midazolam)	FBSS	26	✓							✓	✓		✓		
Kumar et al.(10)	2002	Morphine	Failed back surgery syndrome (FBSS)	21													✓
Anderson et al.(11)	2003	Morphine	FBSS	27	✓		✓	✓		✓		✓	✓		✓		✓
Deer et al.(70)	2004	Not reported	Low back pain	136	*							✓			✓		
Thimineur et al.(8)	2004	Morphine, hydromorphone, fentanyl, methadone	Unspecified	44	*				*	*	✓	✓			✓		
Reden and Anders(12)	2006	Not reported	Not reported	1,647													✓
Shaladi et al.(71)	2007	Morphine	Osteoporotic vertebral fracture	24	✓	✓	✓		✓			✓	✓		✓		
Total				**2,081**	**7**	**6**	**7**	**6**	**2**	**1**	**4**	**10**	**10**	**8**	**13**	**0**	**4**

* These outcomes were reported by these studies but excluded from the analysis for various reasons provided in the *Results* section. Their outcomes data are provided in Appendix D.

** NA: Not applicable. Cost model

Results Synthesis

Effectiveness and Safety

Patient Characteristics

Patient Enrollment Criteria

All 13 included case series on effectiveness and safety limited enrollment to individuals with CNCP for which more conservative pain control measures had provided insufficient relief or unacceptable side effects. Key study protocols of these studies and characteristics of patients enrolled in them are summarized in Table 34 of Appendix C.

In addition to stipulating that only individuals who had lack of success with conservative pain control methods, some also stipulated that participants not be appropriate candidates for surgery or other treatments that could relieve their pain.(7,39,66) Eight required all patients to have successful intraspinal trial results (where defined, typically at least a 50% reduction in pain).(6,8,11,39,66,68,69,71) Eight screened out patients with psychological conditions likely to reduce response to treatment, such as personality disorder, psychosis, and substance addiction or abuse.(8,11,39,65,66,68,69,71) For inclusion and exclusion criteria of the included studies, refer to Table 35 of Appendix C.

Studies' patient enrollment criteria were generally consistent with the indications and contraindications for use of an implantable infusion pump in patients with CNCP described in the *Background* section. These criteria include having a definable cause of pain for which available conservative therapies have been exhausted and surgical correction is not appropriate, and the need for constant (rather than episodic) pain control. In addition, patients must undergo a successful infusion trial, pass a psychological examination, and have no contraindications to undergo surgical implantation of the pump.

Characteristics of Enrolled Patients

The 13 case series enrolled a total of 413 patients. Number of patients enrolled in each study ranged from 11 to 30. Primary pain conditions included:

- Various or unspecified pain types in six studies(6-8,65,66,68)
- Failed back surgery syndrome in four studies(11,55,67,69)
- Low back pain due to any etiology in one study(70)
- Osteoporotic vertebral fracture in one study(71)
- Neuropathic pain in one study(39)

Enrolled patients were in severe pain. Among the studies that reported baseline pain scores on a standard VAS scale (these studies are analyzed under continuous pain outcomes), the weighted baseline mean pain score was 8.7 (SD 2.71) on a scale of 0 to 10, with 0 being no pain and 10 being unbearable pain.

Eight studies did not report the mean duration of time since pain onset, although patients had to meet criteria for minimum pain duration to be diagnosed with chronic pain and enroll in these studies. Of the five studies that did report it, the mean duration of time was 19 months(69), 6.8 years(8), 8 years(6,68), and 9.5 years.(66) In the six studies that reported mean age, it ranged from 44 years(7,66) to 74 years.(71) However, most of the studies reported mean ages in the mid-forties to mid-fifties. Among studies that reported the percentage of women enrolled, it ranged from 35%(66) to 81%(65), and in most studies more women enrolled than men.

A summary of the characteristics of the patients who were enrolled in the studies that are included in this evidence base are provided in Table 36 of Appendix C.

Study Protocols

Of the 13 clinical studies identified, eight (62%) were prospective,(6,8,11,39,55,68-70) three were retrospective (23%),(7,65,66) and for two (15%) it could not be determined whether the study was prospectively or retrospectively designed.(67,71)

Because most studies did not report the number of patients screened before enrollment, it is not possible to determine how highly selected the 413 participants who received an implantable pump were. Patients could be screened out for not meeting study inclusion criteria (discussed above), with only some patients going on to an infused drug trial. Of those undergoing an infused drug trial, not all receive a pump due to poor trial outcomes. Five studies did not report how many potential pump recipients were screened or underwent a trial.(7,55,65,66,71) Only two studies explicitly stated how many patients were screened for inclusion, subsequently underwent an infusion trial, and ultimately received a pump.(11,67) In one of those two studies, 73% of patients referred and 85% of patients who underwent a trial received a pump.(67) In the other, 31% of patients referred and 73% of patients who underwent a trial received a pump.(11) The remaining six studies reported the number of patients who underwent trialing and the number who subsequently received a pump, but did not report the number of patients referred or screened for general inclusion criteria.(6,8,39,68-70) In those studies, the proportion of patients trialed who received a pump ranged from 43%(8) to 87%.(69) See Table 37 of Appendix D for the numbers of patients screened and enrolled for each study that reported that information.

Although 413 patients were initially enrolled in all of the studies included in this report, only seven studies with 143 patients had sufficient reporting and were of sufficient quality to be included in the continuous pain outcome. Similarly, only a few studies reported data for secondary outcomes, including dichotomous pain outcomes, quality of life, functional status, and employment status. Further, all of the studies were small, enrolling only 11 to 30 patients. Whether this leads to a generalizability problem with the data cannot be determined from the currently available information, but the potential is present.

Two studies did not report that they conducted an infusion trial on any patient(65,67), one study only began trials after enrolling half of the patients(7), one study only enrolled patients who had previous unsuccessful intrathecal infusion with different drugs(55), and the rest administered inpatient or outpatient intrathecal or epidural administration trials lasting from a single infusion to weeks.

Nine studies implanted programmable pumps (SynchroMed, Medtronic), one implanted nonprogrammable pumps (Codman, Johnson & Johnson)(71), one implanted either programmable or nonprogrammable pumps(8), and one did not specify the pump type(s) used.(70) Ten studies filled the pumps with morphine. One study also offered sufentanil as an alternative(39), one offered fentanyl only when morphine failed to relieve pain adequately(66), and one also prescribed hydromorphone, fentanyl, and/or methadone.(8) Five studies administered adjuvant drugs intrathecally along with the morphine, such as clonidine(68), bupivacaine(65), tetracaine or bupivacaine(66), bupivicaine, clonidine, or midazolam(69), or clonidine, baclofen, or bupivicaine.(8) The single study that did not administer morphine to any patients enrolled only patients who had failed previous implanted infusion pump therapy with multiple previous intrathecally-delivered drugs.(55) In that study, all patients received methadone. Both the initial and final doses of intrathecally administered drugs administered ranged widely among studies, and among individuals within studies. Some studies allowed patients to continue to take oral adjuvants and oral opioids for breakthrough pain. However, other studies only allowed patients to continue non-opioids. Duration of treatment for which outcomes were reported ranged from six months(55) to 3.5 years.(69)

These protocols for each included study are summarized in Table 37 of Appendix C. A list of studies reporting each outcome is provided in Table 10.

Synthesis of Results

Key Question 1. What is the evidence of efficacy and effectiveness of implantable infusion pumps?

Pain and Pain Relief

Thirteen studies total were identified for Part 1 of this report (efficacy, effectiveness, and safety), however, only nine met inclusion criteria for pain outcomes. Three of the studies were excluded from assessment of pain outcomes for measuring pain with a non-standard scale(7,65,66) and one was excluded from pain outcomes for not reporting a measure of variance or data to impute it to enable analysis.(70)

Continuous Data

Drug infusion with an implantable pump leads to clinically significant pain relief in patients with CNCP. (Strength of evidence: Weak).

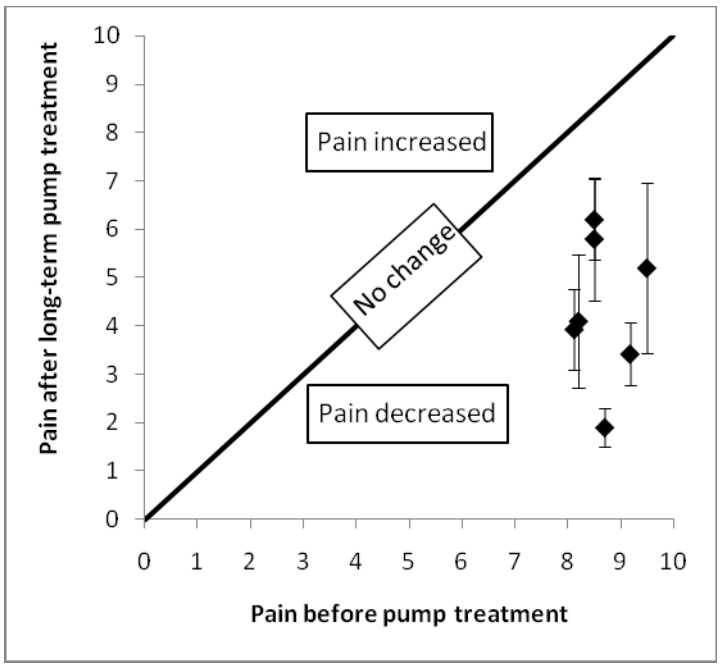
Although we identified nine studies that reported mean pain levels before and during long-term intrathecal administration of opioids with an implanted infusion pump, only seven were analyzed for this outcome because two were excluded for unacceptably low internal validity scores, Thimineur et al.(8) and Anderson and Burchiel.(6) Reasons for the unacceptably low internal validity scores include high rate of attrition (pain scores were reported for only 67% of pump recipients in Anderson and Burchiel), not comparing characteristics of patients who did and did not complete the trial, use of ancillary treatments, subjective outcome measures, and funding from a source with a financial interest in the outcome. Full internal validity assessment of these studies is shown in Table 39 of Appendix D, and extracted data are shown in Table 11 in this section.

Seven studies (n=143) were included in our analysis.(11,39,55,67-69,71) In all studies, opioids were delivered to the intrathecal space by the implanted infusion pump. In six studies, morphine was administered. Three studies administered morphine alone(11,67,71), and three offered alternative or adjuvant drugs.(39,68,69) In the seventh study, only methadone was administered, to patients who had unsuccessful experiences with other intrathecally infused drugs.(55) Four studies enrolled patients with failed back surgery syndrome (FBSS),(11,55,67,69), one enrolled patients with neuropathic pain,(39) one enrolled patients with various causes of noncancer pain,(68) and one enrolled patients with osteoporotic vertebral fractures.(71) The pooled baseline pain score on VAS of 0-10 (with 0 being no pain and 10 being unbearable pain) was 8.7 (SD 2.71), signifying severe pain.

The median internal validity score of these studies is within the low range (Table 39 of Appendix D). Reasons for the low rating varied by study but include the subjectivity of the outcome measure, not comparing the outcomes of patients who did and did not discontinue participation in the study, not screening a consecutive or randomized sample of patients, and use of funding from a source with a potential conflict of interest.

Each individual study showed a statistically significant mean reduction in pain from baseline to longest follow-up point (see Figure 5). Most studies reported pain outcomes for every enrolled patient (i.e., dropouts were not excluded); all included studies reported on at least 89% of patients who received a pump, and the summary estimate includes 98% of patients who enrolled overall.

Figure 5. Average Pain Scores Before and After Treatment with Implantable Infusion Pump for Each Included Study



When the studies were combined in meta-analysis, heterogeneity was substantial ($I^2 = 89.12\%$). To investigate the source of this heterogeneity, we conducted meta-regressions on the following study-level factors:

1. Primary cause of pain
2. Whether preimplantation testing occurred
3. Drug(s) administered
4. Whether pain data were reported for all patients at their last follow-up time point or for only remaining patients at a given follow-up time point (i.e., intent-to-treat basis)
5. Number of patients enrolled
6. Duration of treatment or mean duration of treatment

None of these covariates was significantly associated with pain outcome, but the power of this small evidence base to detect such an effect is limited.

Although the small size of the evidence base limited our ability to thoroughly investigate heterogeneity through subgroup analysis, we had sufficient data to conduct four subgroup analyses. We re-calculated the meta-analyses for:

1. Prospective studies only
2. Patients with failed back surgery syndrome only
3. Patients administered morphine alone only
4. Patients administered morphine with another drug only

None of these subgroups either led to a substantial reduction in heterogeneity, or were significantly different from the meta-analysis that included all seven studies.

The random-effects meta-analysis yielded a SMD of 2.34 (95% CI 1.46 – 3.24). In terms of a VAS of 0-10, it represents a reduction in pain from 8.7 (SD 2.7) at baseline to 3.5 (SD 1.99) when calculated from the SMD using a correlation coefficient of 0.5, and 4.3 (SD 2.71) when the follow-up scores were pooled without correlation to the baseline scores. On average, the patients in these case series went from having severe pain at baseline to moderate pain at longest follow-up. Due to substantial heterogeneity, the point

estimate may not be accurate, and the confidence intervals may represent a more conservative estimate of where the true effect size(s) may lie. However, at a 41% reduction in pain relief, even the lower confidence interval represents a clinically significant reduction in pain.

Additional analyses support the qualitative conclusion that pain is reduced. Sensitivity analysis by manipulation of the correlation coefficient led to a reduction of the estimate to a reduced but still minimally clinically significant reduction in pain. Further, considered in isolation, each of the individual studies reported statistically significant reductions in pain. Impact and cumulative meta-analyses support the conclusion that the therapy is associated with pain reduction (see Table 40 and Table 41 of Appendix D). The impact analysis shows that no single study in the analysis exerts a large influence on any quantitative estimates or upon the qualitative conclusion (Table 41 of Appendix D). Calculated pain outcomes for each study and the results of the meta-analysis are shown in Figure 6 (below).

That this data come from uncontrolled case series should be considered. It is possible that some placebo effect may account for part of the pain relief attained. However, a Cochrane Review that evaluated the influence of placebo interventions for clinical conditions including pain, found a possible placebo effect on reduction of patient-reported pain (although the authors note that it is unclear whether this effect size is clinically importance, and that it cannot be clearly distinguished from other potential sources of bias) The size of this effect was estimated at a SMD of -0.25 (95% CI -0.35 to -0.16), which corresponds to a change in VAS of 6/100 (or 0.6/10).(4,5) This effect size is very small compared with the effect size of change in pre-post pain scores pooled in this analysis.

Although the quantity of pain relief that is experienced cannot be pinpointed due to unexplained heterogeneity, based upon the results of the individual studies and a qualitative assessment of the meta-analysis, we can conclude that pain relief is associated with long-term intrathecal opioid therapy. The reported long-term pain scores represent pooled outcomes of 98% of patients who received an intrathecal pump, suggesting that the reported pain outcomes are representative of the entire study population receiving an infusion pump and are not likely to be biased by patients withdrawing due to insufficient pain relief (see column N = (%) of Follow-up of Table 11). Our meta-analysis found that the amount of pain relief is clinically significant; this qualitative finding was robust to sensitivity analyses.

Table 11. Continuous Pain Score Data

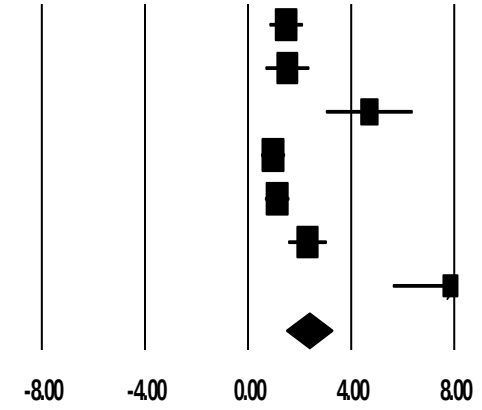
Study	Year	Pain Scale Used*	Baseline Pain Score	Baseline Standard Deviation	N= at Baseline	Baseline Score Range	Longest Follow-up Pain Score	Longest Follow-up Standard Deviation	Follow-up Score Range	n = (%) at Longest Follow-up	*P*-Value	Effect Size Standardized Difference in Means (95% CI)	Duration of Treatment
Shaladi et al.(71)	2007	0-10 VAS	8.7	0.5	24	8 to 10**	1.9	1.0	0 to 5	24 (100%)	<0.001	7.85 (5.60-10.11)	12 months
Thimineur et al.(8)*	2004	0-10 VAS	8.4	1.4	44	Not reported	6.1	0.6	Not reported	38 (86%)	<0.001	1.89 (1.27-2.51)	36 months
Anderson et al.(11)	2003	0-100 VAS	81.2	10.2	27†	Not reported	39.3	21.0	Not reported	24 (89%)	<0.001	2.31 (1.54-3.07)	6 months
Kumar et al.(68)	2001	0-100 VAS	91.8	2.8	16	Not reported	34.2	13.2	Not reported	16 (100%)	<0.001	4.71 (3.00-6.41)	29.14 month mean
Mironer and Tollison(55)	2001	0-10 VAS	8.5	1.1	24	7 to 10	5.8	3.2	1 to 10	24 (100%)	<0.001	0.99 (0.50-1.47)	6 months
Rainov et al.(69)	2001	0-10 VAS	8.2	3.8	26	Not reported	4.1	3.6	Not reported	26 (100%)	<0.001	1.13 (0.64-1.62)	27 months mean
Anderson and Burchiel(6)*	1999	0-100 VAS	78.5	15.9	30	39 to 100	58.5	24.6	Not reported	20 (67%)	0.001	0.93 (0.40-1.45)	24 months
Angel et al.(67)	1998	0-10 VAS	9.5	0.4	11	8 to 10	5.2	3.0	1 to 10	11 (100%)	0.001	1.52 (0.66-2.39)	27 months mean
Hassenbusch et al.(39)	1995	0-10 NRS	8.5	0.92	18	7 to 10	6.2	1.8	2.5 to 9	18 (100%)	<0.001	1.48 (0.81-2.14)	29 months mean
All studies meeting inclusion criteria (Pain scores in terms of a 0-10 VAS. Baseline score from pooled average. Follow-up pain scores in terms of conversion from SMD using correlation coefficient of 0.5 and pooled average (P)			**8.7**	**2.7**	**146**	NA	**3.5 (from SMD) to 4.3 (P)**	**0.72 (P) to 1.99 (SMD)**	NA	**143 (98%)**	**<0.001**	**2.35 (1.46-3.24)**	**Range: 6 months to mean of 29 months**

* VAS Visual analog scale. NRS: Numerical rating scale
** Range provides the minimum and maximum scores and include outliers. Range is not to be construed as a measure of central tendency or average scores, which are the data used to calculate the effect size and p-values.
† Data only reported for 24 completers
‡ NA: Not applicable

Shaded studies not included in analysis due to unacceptably low internal validity scores.

Figure 6. Change in Pain Scores at Longest Follow-up

Studies	Number of Patients Enrolled	Statistics							Standardized Difference in Means and 95% Confidence Interval (CI)	
		Standardized Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	*P*-Value	Pain Scores Lower at Baseline	Pain Scores Lower After Treatment
Hassenbusch et al. 1995(39)	18	1.48	0.34	0.12	0.81	2.14	4.33	<0.00		
Angel et al. 1998(67)	11	1.52	0.44	0.20	0.66	2.39	3.44	0.001		
Kumar et al. 2001(68)	16	4.71	0.87	0.75	3.00	6.41	5.42	<0.001		
Mironer and Tollison 2001(55)	24	0.99	0.25	0.06	0.50	1.47	3.97	<0.001		
Rainov et al. 2001(69)	26	1.13	0.25	0.06	0.64	1.62	4.50	<0.001		
Anderson et al. 2003(11)	24	2.31	0.39	0.15	1.54	3.07	5.91	<0.001		
Shaladi et al. 2007(71)	24	7.85	1.15	1.33	5.60	10.11	6.82	<0.001		
Summary Effect	143	2.35	0.45	0.21	1.46	3.24	5.17	<0.001		



Dichotomous Data

All nine studies that met other inclusion criteria for pain outcomes also had acceptable internal validity scores to be included in these analyses, as shown in Table 42 of Appendix D. The two studies excluded for continuous pain outcomes for internal validity issues had acceptable internal validity scores for this outcome. This is because dichotomous outcomes use the total number of enrolled patients in the denominator and is therefore not susceptible to potential bias due to attrition or failure to compare characteristics of completers and non-completers. Although we assessed the studies for internal validity to ensure that they satisfy minimal criteria for inclusion, we did not rate the strength or stability of these pain outcomes because we consider them secondary to continuous pain outcomes, analyzed in the previous section.

All but two of the studies analyzed in the dichotomous pain outcomes had 100% follow-up at longest duration of treatment. For the two studies that did not, Anderson and Burchiel and Anderson et al., we used the proportion of patients attaining clinically significant pain relief as reported in the articles.

At Least 25% Pain Relief

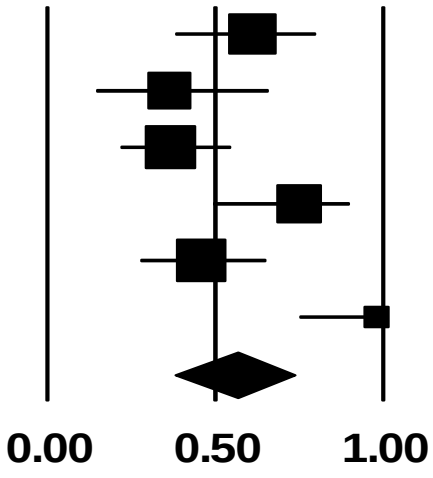
Six studies (n = 123 enrolled) reported the proportion of patients with at least a 25% reduction in pain(6,68) or data to calculate it.(37,62,63,(71) The primary cause of pain was failed back surgery syndrome in three studies,(6,55,67), various causes in one study,(68), osteoporotic vertebral fractures in one study,(71) and neuropathy in one study.(39) Drugs administered were morphine,(6,39,67,68,71) sufentanil citrate(39), clonidine if needed in addition to morphine(68), and methadone.(55) Duration of treatment ranged from six months(55) to a mean of 29 months.(39,68)

The median internal validity score of this evidence base is within the low category (Table 42 of Appendix D). Reasons for low-range scores varied by study and included failure to compare characteristics of completers and non-completers for other outcomes at baseline, use of ancillary treatments, the subjective nature of the outcome, and use of funding from sources with a financial interest in the outcome.

Findings from studies reporting the proportion of patients attaining at least a 25% reduction in pain ranged from 37%(6) to 100%(71) (see Figure 7, below for extracted data) and were substantially heterogeneous ($I^2 = 66.5\%$) when combined in meta-analysis. This heterogeneity was not explained by meta-regression (factors used were the same as for continuous outcomes), although due to the small number of studies there is limited power of the regression to detect a significant effect. We combined these studies in a meta-analysis and estimated that 56.3% (95% CI 33.7%-73.3%) of patients had at least a 25% reduction in pain (Figure 7, below). Because of the unexplained substantial heterogeneity, the point estimate may not be accurate and we therefore consider it unstable and do not draw a quantitative evidence-based conclusion from it. Indeed, more than one point estimate may exist (e.g., for different patient populations or treatment protocols). However, the 95% confidence intervals provide a reasonable range of what proportion of patients attain at least 25% pain relief.

Figure 7. Proportion of Patients with at Least 25% Reduction in Pain

Studies	Number Enrolled	Number with ≥25% Reduction in Pain	Statistics: Proportion	Lower Limit	Upper Limit	Proportion with 95% Confidence Interval (CI)
Hassenbusch et al. 1995(39)	18	11	0.611	0.379	0.802	
Angel et al. 1998(67)	11	7	0.364	0.143	0.661	
Anderson and Burchiel 1999(6)	30	11	0.367	0.216	0.549	
Kumar et al. 2001(68)	16	12	0.750	0.492	0.903	
Mironer and Tollison 2001(55)	24	11	0.458	0.275	0.654	
Shaladi et al. 2007(71)	24	24	0.980	0.749	0.999	
Meta-analysis Summary Effect Size	123	-	0.563	0.377	0.999	



At Least 50% Pain Relief

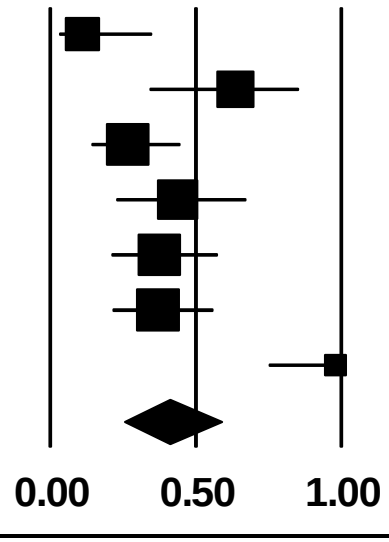
Seven studies (n = 150 enrolled) reported the proportion of patients who had at least a 50% reduction in pain scores or data to calculate the proportion. Patients were given morphine in six studies(6,11,39,67,68,71), an alternative of sufentanil in one of those studies,(39) clonidine in addition to morphine if needed in another one of the morphine studies(68), and methadone in the fifth study.(55) Patients had chronic pain due to failed back surgery syndrome in four studies,(6,11,55,67) osteoporotic vertebral fractures in one study,(71) pain due to various causes in one study,(68) and exclusively neuropathic pain in the remaining study.(39) Duration of treatment ranged from six months(55) to a mean of 29 months.(39,68)

The median internal validity score of this evidence base is within the low range (Table 42 of Appendix D). Reasons for low-range scores varied by study and included failure to compare characteristics of completers and non-completers for other outcomes at baseline, use of ancillary treatments, the subjective nature of the outcome, and use of funding from sources with a financial interest in the outcome.

Proportion of patients who attained at least a 50% reduction in pain from baseline ranged from 11%(39) to 100%;(71) see Figure 8 below for data. When the studies were combined in a meta-analysis, substantial heterogeneity was detected ($I^2 = 67.6\%$). This heterogeneity was not explained by meta-regression (factors used same as for continuous outcomes). A random-effects meta-analysis estimated that 40.8% (95% CI 25.2%-58.5%) of CNCP patients had at least a 50% reduction in pain with intrathecal opioid use. This heterogeneity was not explained by meta-regression (factors used same as for continuous outcomes), although the small number of studies limits the power of the regression to detect a significant effect. Because of the unexplained substantial heterogeneity, the point estimate may not be accurate and we therefore consider it unstable and do not draw an evidence-based quantitative conclusion from it. The 95% confidence intervals provide a reasonable range of what proportion of patients attain at least 50% pain relief.

Figure 8. Proportion of Patients with at Least 50% Reduction in Pain

Studies	Number Enrolled	Number with ≥25% Reduction in Pain	Statistic: Proportion	Lower Limit	Upper Limit	Proportion with 95% Confidence Interval (CI)
Hassenbusch et al. 1995(39)	18	2	0.111	0.028	0.352	
Angel et al. 1998(67)	11	7	0.636	0.339	0.857	
Anderson and Burchiel 1999(11)	30	8	0.296	0.156	0.490	
Kumar et al. 2001(68)	16	7	0.438	0.225	0.676	
Mironer and Tollison 2001(55)	24	9	0.375	0.208	0.578	
Anderson et al. 2003(11)	27	15*	0.625	0.422	0.792	
Shaladi et al. 2007(71)	24	24	0.980	0.749	0.999	
Meta-analysis Summary Effect Size	150	--	0.408	0.252	0.585	



*Assuming that the three patients who withdrew from the study did not experience this outcome

Discontinuation from Clinical Study due to Insufficient Pain Relief

Of patients who began treatment with an implantable pump used for intrathecal opioid delivery for CNCP, 8.0% (95% CI 3.8%-15.8%) discontinued treatment in the clinical trial due to insufficient pain relief. (Stability of evidence: Low)

Five studies (n = 102 enrolled) on intrathecally-administered opioids reported discontinuation from clinical study due to insufficient pain relief.(6,11,39,67,68) All studies administered strong opioids—usually morphine(6,11,39,67,68), in one study with clonidine if needed(68) and in another study with sufentanil citrate as an alternative.(39) Primary causes of pain included neuropathic pain(39), pain due to failed back surgery syndrome(6,11,67), and pain due to various causes.(68) Four of these studies used an infusion trial in all candidates who met general inclusion criteria to select patients most likely to benefit from implantation of an infusion pump(6,11,39,68), while one did not.(67) Duration of treatment ranged from 6 months(11) to a mean of 29 months.(39,68)

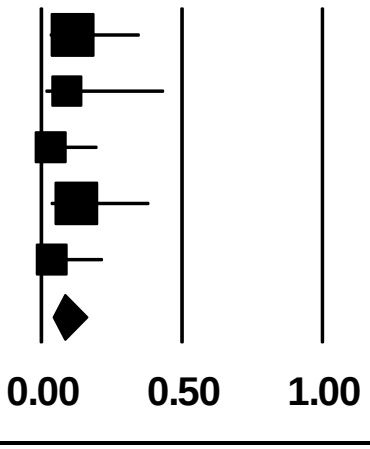
These studies had a median internal validity score within the low range (Table 43 of Appendix D). Reasons for the low rating varied by study and included use of ancillary treatments in a substantial portion of the population and use of funding from a source with a potential conflict of interest.

Data extracted from these studies are shown in Figure 9, below. Percentage of patients who discontinued participating in the clinical trials ranged from 3%(6) and 13%(68), and no more than two individuals per study withdrew from each trial for this reason. These studies ranged in duration of treatment from six months to a mean of 29 months.

When the studies were combined in a meta-analysis, no substantial heterogeneity was detected (I^2 <0.001%). A random-effects meta-analysis found a rate of discontinuation from clinical study of 8.0% (95% CI 3.8%-15.8%). This meta-analysis is shown in Figure 9, below. This figure was robust to sensitivity analyses and can be considered quantitatively stable.

Figure 9. Proportion of Patients who Discontinued due to Insufficient Pain Relief

Studies	Number of Patients Enrolled	Number of Patients who Discontinued	Statistics: Proportion Discontinued	Lower Limit	Upper Limit	Proportion Discontinued with 95% Confidence Interval (CI)
Hassenbusch et al. 1995(39)	18	2	0.111	0.028	0.358	
Angel et al. 1998(67)	11	1	0.091	0.013	0.439	
Anderson and Burchiel 1999(6)	30	1	0.033	0.005	0.202	
Kumar et al. 2001(68)	16	2	0.125	0.031	0.386	
Anderson et al. 2003(11)	27	1	0.037	0.005	0.221	
Meta-analysis Summary Effect Size	102	-	0.080	0.038	0.158	



Quality of Life

It is not possible to determine whether long-term use of intrathecal opioids change the quality of life for patients with CNCP, because the two studies that met inclusion criteria for this outcome had inconsistent findings (one found improvement, but the other did not).

Our searches identified three studies that reported long-term quality of life outcomes in patients that received an implantable infusion pump for CNCP.(55,71) However, one of these studies, Thimineur et al.,(8) was found to have an unacceptably low score upon assessment of internal validity and are therefore not considered in the analysis (however, data from this study is provided in Table 12, below). Reasons for the unacceptably low score included high rate of attrition not comparing characteristics of patients who did and did not complete the trial, which is important for a case series with only 86% follow-up, use of ancillary treatments, and subjective outcome measures. Full quality assessment of this study is shown in Table 44 of Appendix D.

Two studies (n = 48) remained for analysis.(55,71) In one study, infused methadone was studied in patients with failed back surgery syndrome.(55) In the other, infused morphine was studied in patients with osteoporotic vertebral fractures. The evidence base was rated as low in internal validity overall. Failure to use objective outcome measures, to report whether all or consecutive patients were enrolled, and to specify the funding source were factors in one or both studies that compromised the score. A full internal validity assessment is shown in Table 44 of Appendix D.

The studies had qualitatively inconsistent findings. Mironer and Tollison (2001)(55) measured the quality of life in 24 patients with failed back surgery syndrome using the Tollison Quality of Life Scale and did not observe a change in categorization of the quality-of-life scores after six months of treatment. Shaladi et al.(71) administered the Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) to 24 patients with osteoporotic vertebral fractures and found a dramatic improvement in quality of life after one year of treatment. We therefore found the evidence to be inconclusive. Scores for this outcome and calculated *P*-values and SMDs for each study are shown in Table 12, below.

Because the findings of the studies differ, we can draw no evidence-based conclusions for this outcome. It is unclear why the findings of these studies differ; there are too few studies to investigate heterogeneity. Possible explanations include differences in patient population and treatment protocols, as well as the instrument used to measure quality of life.

Table 12. Quality of Life Data

Scale Used	Study	Baseline Mean Score	Standard Deviation	N = at Baseline	Baseline Score Range	N= (% of baseline) at Follow-up	Follow-up Mean Score	Follow-Up Standard Deviation	Follow-up Score Range	Longest Follow-up Time	Standardized Mean Difference (95% CI)	*P* =
Tollison Quality of Life Scale	Mironer and Tollison 2001(55)	66.9	20.4	24	30 to 104	24 (100%)	63.08	23.2	18 to 99	6 months	0.170 (-0.233 to 0.573)	0.409
Short Form 36 (SF-36)	Thimineur et al. 2004(8)	16.2	12.4	44	NR	38 (86%)	11.1	17.6	NR	36 months	0.326 (-0.001 to 0.652)	0.050
Questionnaire of the European Foundation of Osteoporosis (QUALEFFO)	Shaladi et al. 2007(71)	114.6	10.4	24	81 to 126	24 (100%)	79.13	13.43	50 to 101	12 months	2.91 (1.99 to 3.82)	<0.001

NR Not reported

Shaded studies excluded from analysis due to unacceptably low internal validity scores

Functional Status

Because only one study reported this outcome, there was an insufficient quantity of evidence to permit a conclusion for this outcome.

Our searches identified three studies that reported long-term functional status outcomes in patients that received an implantable infusion pump for CNCP.(8,11) However, two of these studies, Anderson and Burchiel(6) and Thimineur et al.(8) were found to have an unacceptably low score upon assessment of internal validity and are therefore not considered in the analysis (however, data from these studies are provided in Table 13 of Appendix D). Reasons for the unacceptably low score differed between the studies and included high rate of attrition (functional status data were reported for only 67% of pump recipients in Anderson and Burchiel), not comparing characteristics of patients who did and did not complete the trial, use of ancillary treatments, subjective outcome measures, and funding from a source with a financial interest in the outcome. Full quality assessment of these studies is shown in Table 45 of Appendix D.

The remaining study, Anderson et al.(11), was rated as low in quality (Table 45 of Appendix D). Reasons for the overall low quality rating include not comparing characteristics of completers and non-completers, use of ancillary treatments, and use of subjective outcome measures.

Anderson et al. assessed functional status in 24 patients predominantly with failed back surgery syndrome before and during treatment with intrathecal morphine using the short-form Sickness Impact Profile (s-SIP), and reported a statistically significant improvement at six months. Although this study reported a statistically significant mean improvement in functional status and a pre-post SMD of 1.15 (95% CI 0.637-1.669) that suggests a clinically large effect size, data from one study with low rated internal validity provides insufficient evidence to allow evidence-based conclusions. Further, potential for bias exists when only a small proportion of an overall evidence base report a particular outcome. Therefore, no conclusions can be drawn for this outcome. The data from this study and *P*-values and SMD calculated from it are shown in Table 13, below.

Table 13. Functional Status

Study	Screening Method and Number of Patients	Scale	Baseline Mean Score	Baseline SD	Baseline Score Range	Longest Follow up Mean Score	Longest Follow up SD	Longest Follow-up Score Range	SMD (95% CI)	*P*-value	Duration of Follow Up
Thimineur et al. 2004(8)	Intrathecal trial (n = 44 at enrollment and 38 at follow-up)	Oswestry Disability Index (ODI)	31.5	5.6	Not reported	27.0	9.3	Not reported	0.555 (0.213 to 0.896)	0.001	36 months
Anderson et al. 2003(11)	Epidural trial (n = 14 at enrollment and follow-up)	Short-form Sickness Impact Profile (s-SIP)	14	5	Not reported	7	5	Not reported	1.400 (0.663 to 2.137)	<0.001	6 months
	Intrathecal trial (n = 10 at enrollment and follow-up)	Short-form Sickness Impact Profile (s-SIP)	16	3	Not reported	12	6	Not reported	0.770 (0.064 to 1.475)	0.033	
	All patients (n = 24 at enrollment and follow-up)	Short-form Sickness Impact Profile (s-SIP)†	14.8	4.3	Not reported	9.1	5.4	Not reported	1.15 (0.637 to 1.669)	<0.001	
Anderson and Burchiel 1999(6)	Unspecified spinal infusion (n = 30 implanted, 20 at follow-up)	Chronic Illness Problem Inventory (CIPI) - Total	26.9	9.5	Not reported	27.25	13.15	Not reported	0.030 (-0.409 to 0.468)	0.894	24 months
		CIPI-Sleep	2.53	1.10	Not reported	1.45	1.12	Not reported	0.973 (0.441 to 1.505)	<0.001	
		CIPI-Social Activities	2.28	1.01	Not reported	1.78	1.13	Not reported	0.465 (0.004 to 0.926)	0.048	

Study	Screening Method and Number of Patients	Scale	Baseline Mean Score	Baseline SD	Baseline Score Range	Longest Follow up Mean Score	Longest Follow up SD	Longest Follow-up Score Range	SMD (95% CI)	*P*-value	Duration of Follow Up
		CIPI-Medications	2.18	1.19	Not reported	1.71	1.56	Not reported	0.333 (-0.117 to 0.783)	0.147	
		CIPI-Inactivity	1.43	0.70	Not reported	1.05	0.92	Not reported	0.457 (-0.004 to 0.917)	0.052	

SD Standard deviation.
SMD Standardized mean difference.

† Data for this set calculated by ECRI Institute.

Shaded studies excluded from analysis due to unacceptably low internal validity scores

Employment Status

The current evidence is insufficient to determine whether implantable infusion pumps are associated with a change in employment status among patients with chronic noncancer pain.

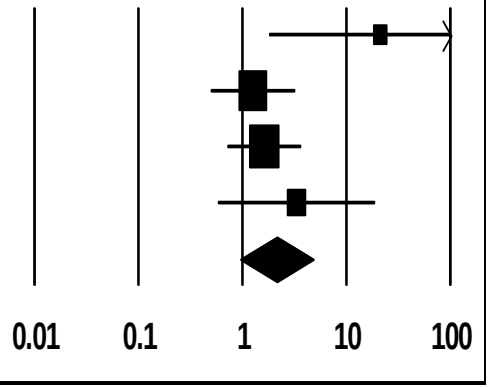
Our searches identified four studies (n = 115 enrolled) that compared the proportion of a total of 83 patients working or otherwise appropriately occupied (e.g., homemaker, student, retired for reasons other than pain) before and after implantation.(6,7,39) Only 83 of the 115 enrolled patients were considered eligible for employment by the study authors. These studies enrolled patients with CNCP due to various or unspecified causes,(7,8,66) or various conditions with failed back surgery syndrome being the most frequent cause. All of the studies administered morphine. Two offered an alternative of fentanyl(8,66), and one of those studies also offered alternatives of hydromorphone or methadone.

The internal validity assessment of these studies is shown in Table 46 of Appendix D. Overall, the evidence base was rated as low. Factors limiting the score differed by study but included financial interest of funders in outcome, lack of reporting on patient selection methods, and the treatment of a large portion of patients with ancillary treatments. As only a subset of studies that report efficacy and harms measures reported employment status, the findings from these studies should be interpreted with caution because of the potential for bias.

All four studies reported improvements in employment rates. However, not all studies reported statistically significant improvements in employment rates. We combined these three studies in a random-effects meta-analysis. Heterogeneity was not substantial ($I^2 = 38.6\%$) In these studies, the odds ratio of working after pump implantation compared to working before implantation is 2.12 (95% CI 0.941-4.767), a change that is not statistically significant ($P = 0.070$) and encompasses the possibility that employment status is higher, lower, or the same after pump placement. Further, when only a subset of studies report a certain outcome, potential for bias exists. Therefore, we do not draw any conclusions regarding whether employment rates are increased after pump implantation. This analysis is illustrated in Figure 10 below, along with data used to generate it.

Figure 10. Change in Employment Status

Studies	Number Enrolled	Number (%) Fully Employed at Baseline	Number (%) Fully Employed at Study End	Statistics: Odds Ratio	Lower Limit	Upper Limit	*P*-Value	Odds Ratio with 95% Confidence Interval (CI): More Recipients Employed Before / More Recipients Employed After
Kanoff 1994(7)	15	0/15 (0%)	6/15 (40%)	21.21	1.79	251.56	0.015	
Tutak and Doleys 1996(66)	26	5/26 (19%)	6/26 (23%)	1.26	0.49	3.24	0.632	
Anderson and Burchiel 1999(6)	30	16/30 (53%)	13/20* (65%)	1.62	0.84	6.48	0.250	
Thimineur et al. 2004(8)	44	1/22** (5%)	3/22 (14%)	3.32	0.03	4.86	0.180	
Meta-Analysis Summary Effect Size				2.12	0.941	4.767	0.070	



* Number remaining at follow-up
** Number considered eligible for employment

Use of Other Medications and Other Treatments

We collected and report relevant information regarding the use of medications and treatments in addition to infusion pump treatment but did not rate the internal validity or strength or stability of this evidence because the following two factors may exert substantial influence on the use of medications and other treatments without regard to patients' pain levels:

- Clinical study protocols
    - The use of medications and treatments in addition to pump infusion is primarily dependent upon the protocols of each study. In some studies, other medications and treatments for pain were prohibited. In other studies, other medications and treatments were allowed selectively, or without restriction. Therefore, the use of medications and treatments in this evidence base may not collectively provide a meaningful surrogate for pain outcomes.
- Indications
    - In some instances it may be unclear why a patient is taking a certain medication, as some medications have multiple indications. For instance, some individuals may continue to take tricyclic antidepressants for control of depression rather than neuropathy.

Intrathecal administration of opioids by implantable pump was associated with an overall decrease in the quantity of other drugs taken or a decrease in the proportion of patients taking other drugs.

Nine studies reported use of other medications in a total of 347 implantable pump recipients.(6-8,11,39,67-69,71) Due to differences in reporting among the studies, their findings could not be combined in a meta-analysis or otherwise quantitatively summarized. Some studies reported adjunctive treatment use in terms of number of patients receiving it, while others noted the number of patients who used adjunctive treatments but did not quantify how much, and not all reported what type of medications were used. One study reported the outcome in terms of the Medication Quantification Scale (MQS).

Despite the differences in ways that use of other medications was measured, all nine studies reported that the number of patients using medications or the total quantity of medications decreased from baseline to longest follow-up. Notably, two studies even reported that pump recipients used no oral or transdermal medications at all.(69,71) For a summary of the findings of all nine studies, refer to Table 47 of Appendix D.

Changes in Quantity of Infused Medication Administered

Quantity of medication administered may be considered a surrogate outcome for pain or the development of drug tolerance. However, we did not assess the internal validity of the data or rate the strength and stability of the findings because the actual relationship between the quantity of medication administered and treatment success or failures is unclear. Although tolerance and hyperalgesia are potential causes of dose escalation that cause the most concern, additional confounding factors include:

- Titration
  - Opioids are typically slowly titrated to achieve maximal pain control with minimal adverse effects. Initial doses do not, therefore, represent a full therapeutic dose. Rather, they are a starting point from which therapy can be tailored.
- Differences in prescribing preferences
  - Attitudes toward prescribing may vary among specialist types, countries in which the study is conducted, and individual clinicians. Dose and dose escalation may largely reflect these clinical preferences rather than the state of patients' pain
- Progression of underlying disease
  - The painful disease for which the patient is seeking treatment may progress, causing a worsening of pain that in turn prompts increase in dose required. This is probably especially true for diseases known for their progressiveness, such as degenerative and osteoporotic diseases or diabetic neuropathy.
- Unclear causal relationship between pain levels and quantities of medication
  - It is possible that patients may have lower pain scores because they are receiving more opioid, or that patients may receive more opioid because they have higher pain levels.

The dose of medication infused by an implantable infusion pump increased over time, but the amount of dose change is not predictable from available studies.

We did not rate the strength or stability of this conclusion because of the confounding influence of factors including titration, differences in prescribing preferences, progression of underlying disease, and unclear causal relationship between pain levels and quantities of medication.

Ten studies that enrolled a total of 218 patients reported dosage at one or more long-term treatment follow-up times. Eight studies reported doses of morphine or morphine equivalent/equianalgesic dose.(6,11,65-69,71) One study reported on dosing of methadone(55), and one reported on dosing of sufentanil.(39) The data extracted from these studies are shown in Table 48 of Appendix D.

All studies reported increases in drug administered after baseline. No conclusions can be drawn regarding dose escalation associated with methadone or sufentanil, as only one study addressed each of these drugs. The remaining text in this section will pertain to the eight studies that reported the use of morphine or equivalent. The increase in dose over time for these studies is shown in Figure 11. Five of these studies only reported baseline and one follow-up time (Shaladi et al., Anderson and Burchiel, Angel et al., Anderson et al., Krames and Lanning), so the changes in the quantity of intrathecal opioid administered appears to be increasing linearly, although that may not actually be the case. The two studies with more than three time points (Tutak and Doleys, Rainov et al.) show a dosage increase pattern that plateaus. The dose of drug administered at baseline (Figure 12) or last recorded follow-up time (Figure 13) do not appear to be related to mean VAS scores. Data on the changes in quantity of intrathecal drug infused are shown along with other study protocols in Table 36 of Appendix C.

Figure 11. Changes in Quantity of Intrathecal Opioids Over Time

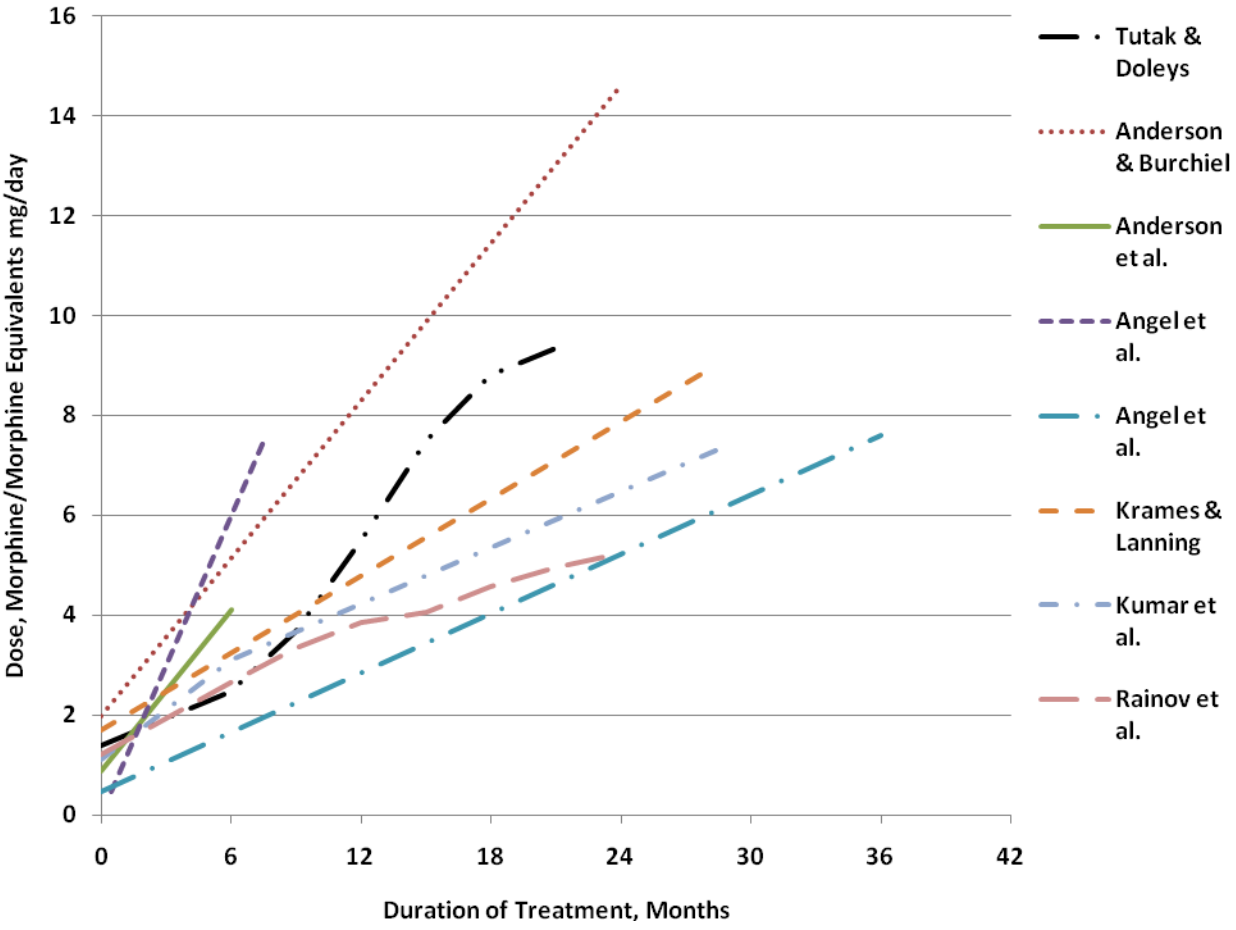


Figure 12. Initial Dose and VAS Pain Score

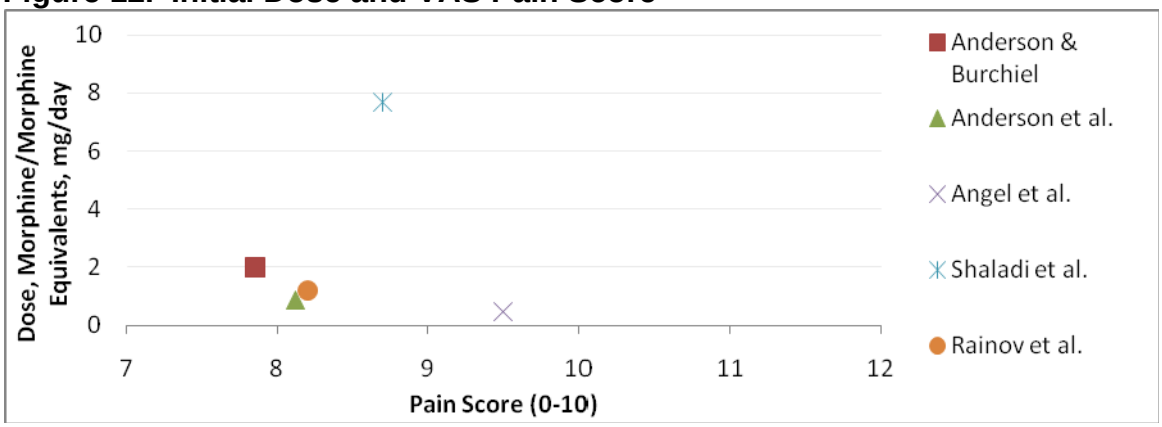
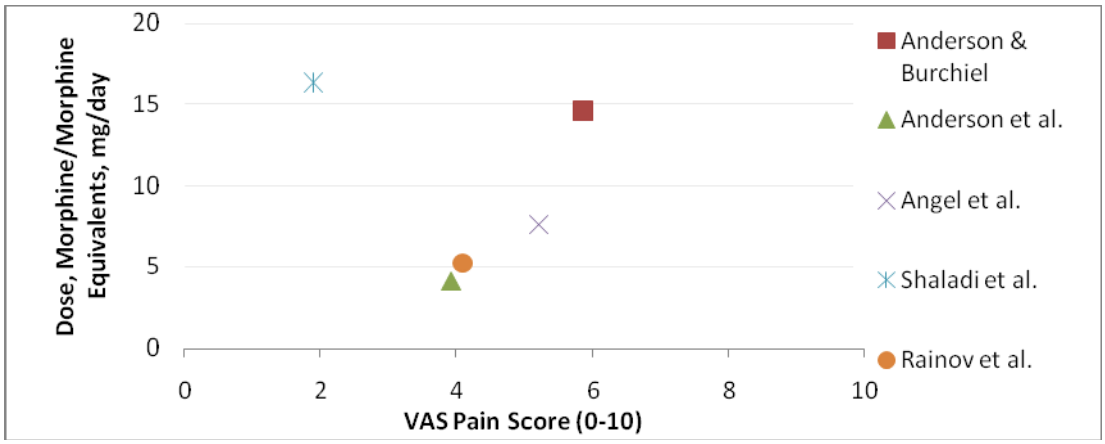


Figure 13. Dose and VAS at Last Data Collection Point



Key Question 2. What is the safety profile of implantable infusion pumps?

Data from Case Series

Discontinuation from Clinical Study due to Adverse Events

Of patients with CNCP who begin intrathecal opioid therapy with an implanted pump, 8.3% (95% CI 4.4% to 15.1%) of patients discontinued treatment due to adverse events and effects. (Stability of estimate: Low).

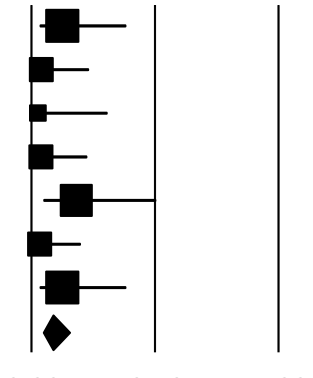
Seven studies (n = 132 enrolled) on intrathecally-administered opioids reported the number of patients who discontinued participating in clinical study due to adverse events.(6,7,39,65-68) Drugs administered included morphine alone(6,7,67), morphine with or without bupivacaine(65) or clonidine(68), or with sufentanil citrate(39) or fentanyl(66) as an alternative. Patients had neuropathic pain alone,(39) failed back surgery syndrome,(6,67) pain due to various or unspecified causes.(7,65,66,68) All pump candidates meeting general inclusion criteria underwent a trial infusion in four studies.(6,39,66,68) In one study, only some pump candidates had an infusion trial,(7) and in two, no candidates underwent a trial.(65,67) Mean duration of follow-up ranged from 17 months(7) to 29 months.(39,68)

The median internal validity score of this evidence base was within the low range (Table 49 of Appendix D). Reasons for the low rating vary by study and include not using objective inclusion criteria, not comparing the characteristics of completers and non-completers (to identify whether the patients who discontinued due to adverse events differed in some way at baseline from patients who continued), and use of funding from sources with potential conflict of interest.

Data from each study are shown in Figure 14, below. Each clinical study enrolled 11 to 30 patients, and in each study, 0 to 2 patients withdrew due to adverse events. Zero percent(39) to 13%(65) of enrolled patients per trial discontinued treatment due to adverse events. At longest duration of treatment (6 months—mean of 29 months), 8.3% (95% CI 4.4% to 15.1%) of patients discontinued participation in intrathecal treatment studies (see Figure 14, below). All sensitivity analyses were robust. The rate was not significantly different when only the studies that used infusion trials to select pump recipients were analyzed (5.9% [95% CI 2.4%-14.1%], I^2 <0.001) or when only the studies that did not use infusion trials for all pump candidates were analyzed (11.4% [95% CI 4.8%-24.8%], I^2 <0.001).

Figure 14. Discontinuation from Clinical Study due to Adverse Events

Studies	Number of Patients Enrolled	Number of Patients Discontinued	Statistics			
			Proportion who Discontinued	Lower Limit	Upper Limit	Discontinuation Rate with 95% Confidence Interval (CI)
Krames & Lanning 1993(65)	16	2	0.125	0.031	0.386	
Kanoff 1994(7)	15	1	0.067	0.009	0.352	
Hassenbusch et al. 1995(39)	18	0	0.026	0.002	0.310	
Tutak and Doleys 1996(66)	26	1	0.038	0.005	0.228	
Angel et al. 1998(67)	11	2	0.182	0.046	0.507	
Anderson and Burchiel 1999(6)	30	1	0.033	0.005	0.202	
Kumar et al. 2001(68)	16	2	0.125	0.031	0.386	
Meta-analysis Summary Effect Size	132	-	0.083	0.044	0.151	



Adverse Events

No serious drug-related adverse events or effects were reported by the clinical trials. However, serious pump-related events, primarily reoperation due to pump technical failure, were reported.

The variability in methods for reporting adverse events, failure to report the absence of unobserved but potential adverse events in some studies, inconsistent reporting or use of definitions of events, and absence of control groups precluded our pooling of adverse events data from the case series meeting inclusion criteria for meta-analysis. Adverse events were typically listed but details regarding the severity, duration, and time of appearance of the event were typically not reported.

The 231 patients enrolled in the 13 case series that reported adverse events were being treated for CNCP due to various causes(7,8,65,66,68), failed back surgery syndrome,(6,11,55,67,69) neuropathic pain(39), low back pain(70) or osteoporotic vertebral fracture.(71) In eight studies, morphine alone,(6,7,11,67,71) or with or without bupivacaine(65) or clonidine(68) or bupivacaine, clonidine or midazolam(69) was administered. Alternative drugs were administered in some studies, including sufentanil citrate,(39) fentanyl,(66), and hydromorphone, fentanyl, or methadone.(8) In the study that did not administer morphine, methadone was administered.(55) One study did not report drug administered.(70)

We divided the adverse events into two general categories: drug-related and device-related. The most commonly reported drug-related adverse events included gastrointestinal effects (e.g., constipation, nausea, dyspepsia), headache, fatigue/lethargy/somnolence, and urinary complications (e.g., retention, hesitancy, "disturbance"). These adverse events are typical of patients taking opioids by any mode of administration. No apparently life-threatening opioid-related adverse events, such as respiratory depression or sedation, were reported.

Based upon these reports, it is not possible to determine the severity of many adverse events such as headache or nausea, or whether adverse events and effects were successfully managed medically or whether they abated over time with acclimation to the drug. All opioid-associated adverse events and effects reported in the 13 studies are reported in Table 50 of Appendix D.

We present data on opioid addiction and abuse in Table 51 of Appendix D, because of the heightened medical and societal concern regarding these outcomes in patients taking opioids long-term. Only one patient with a symptom suggestive of opioid addiction, drug-seeking behavior, was reported.(6) Treatment was discontinued for that patient, but from the report it is unclear whether substance abuse or addiction was actually diagnosed or how that patient was subsequently treated.

Device-related adverse events include pump and catheter malfunctions and malpositioning, surgical complications, and post-surgical complications. Where reported, the percentage of patients who required reoperation for device complications during the follow-up period ranged from 9%(67) to 42%.(66) All device-related adverse effects and events reported by the case series are reported in Table 52 of Appendix D.

In addition, seven deaths were reported in three studies. In one study, a patient died during elective coronary angioplasty.(7) In the second study, one patient died due to suicide, another due to myocardial infarction, and a third due to unknown cause.(8) It is unclear whether the suicide or death due to unknown cause was possibly pump- or opioid-related. In the third study, one patient died due to chronic obstructive pulmonary disease, another died due to pericolonic abscess, and a third died due to myocardial infarction, none of which were considered treatment-related.(6)

Data from MAUDE Reports

We also searched the Food and Drug Administration's (FDA) MAUDE for adverse event reports for intrathecal pumps between 1996 and late February 2008.

When reading this section, recognize that MAUDE data has limitations:

1. Because the total number of implanted infusion pumps in the United States is not known, the reports of these events should not be construed to be indicative of the rate of any event(s). Regardless of the number of reports, the actual rate of any adverse event may be high, low, or anywhere in between.
2. These adverse event reports are on the use of implantable infusion pumps for any indication, including cancer pain and spasticity. Implanted infusion pumps may have different harms profiles in different patient populations, and these findings should not necessarily be generalized to patients with CNCP.
3. The severity of the event was not always reported.
4. The duration of the event is typically not reported
5. Whether event was successfully medically or surgically managed is not always reported
6. It is not always possible to definitively attribute the event to the pump or associated human error, based upon these reports. Underlying conditions, co-morbidities, and other medications could have produced many of the nonspecific health outcomes.

A total of 975 relevant reports were identified in MAUDE using a sensitive filter comprised of textwords. Many serious events and effects, including paralysis and death, were reported.

An unfiltered search of the FDA MAUDE database yielded 9,082 reports (Table 14). ECRI Institute applied several filters reports to identify the most relevant reports (for example, filtering for any mention of "intraspinal"or "intrathecal" or other spine-related term; see Appendix A for more details); a total of 975 relevant reports were identified. However, it is impossible to determine the rate of adverse events associated with intrathecal pumps from this data because it is unclear how many people in the United States actually have or have had a pump. Medtronic's Web site reports that "over 50,000" individuals have received one of their pumps, but it is unclear how current the figure is (date of estimate not noted on Web site), how many of these persons reside in the U.S., how current the figure is or how many additional people have pumps made by other manufacturers.(82) A 2005 analysis of MEDSTAT MarketScan data estimated that there are "approximately 100,000 Americans with neuropathic pain and an IT implanted pump."(83) This estimate was based on observing 1605 patients per year using an intrathecal pump for neuropathic pain during 2000-2001 within a database of four million patients. However, the number of Americans with pumps for other indications remains unclear.

Most importantly, 53 deaths were reported. Most frequently, the deaths were due to unknown causes (15 cases). The other most common causes were cardio/pulmonary arrest (7 cases), cardiac disease (5 cases), and overdose (5 cases). Causes of death and number of reports are listed in Table 54 of Appendix D.

The highest number of serious and potentially serious reports were infection (128 reports), inflammatory mass(es) (83 reports), respiratory difficulty (28 reports) and paralysis (20 reports). The most frequently reported device-related event was re-operation due to pump or catheter failure (405 reports), followed by removal of the device without replacement (211 reports). All other device-related events had fewer than 100 instances, and included non-operative equipment revision (86 reports), operator error (e.g., incorrect pump programming) (35 reports), and planned device replacement due to battery expiration (26 reports). The number of reports per serious adverse event and adverse events experienced by 50 patients or more are presented in Table 53 of Appendix D. Miscellaneous causes (e.g., limb numbness, nausea) experienced by fewer than 50 individuals per adverse event/effect are listed in Table 55 of Appendix D.

We divided the event reports by patient health outcome (e.g., infection, edema, insufficient pain relief) and device-related events (e.g., pump or catheter failure, surgical error during implantation). We used the term 'health outcome' to label the category of health effects that may be caused by drug administered because it wasn't always possible to definitively attribute the effect to a drug. In many instances, more

than one event was reported in a report, and more than one event occurred per patient. For this reason, the number of events in our tables total to more than 975.

Table 14. Unfiltered Count of FDA MAUDE Reports 1996 to 2007 for Implantable Infusion Pumps

Year	Death	Serious Injury	Malfunction	Other	Invalid Data	Total
1996	3	23	16	3	0	45
1997	10	106	110	66	2	294
1998	12	116	110	93	1	332
1999	7	58	155	42	5	267
2000	12	80	188	87	0	367
2001	20	198	344	249	10	821
2002	29	244	570	185	14	1,042
2003	53	363	386	287	4	1,093
2004	24	555	137	292	5	1,013
2005	44	567	188	426	5	1,230
2006	80	914	353	432	10	1,789
2007 first half	49	593	135	12	0	790
Total	**343**	**3,817**	**2,692**	**2,174**	**56**	**9,082**

Note: Based on a 2008 search, ECRI Institute filtered MAUDE reports for relevance using search terms described in Appendix A, resulting in the count of 975 relevant MAUDE reports described in this section.

Additional Information

In this subsection, additional information regarding important adverse events not captured by the case series is described.

Early Mortality: In a span of four months (December 2005 and March 2006) nine patients died within three days of pump implantation, as reported to Medtronic. Based upon these reports, Medtronic estimated the rate of early death after initiation of intrathecal infusion therapy to be 1 in 1,000. This rate suggests that there are 27,000 pumps implanted annually for intrathecal drug delivery. Medtronic notes they became aware of the increase in rate of early report deaths in February 2006, but it is unclear how many total patients received pumps or how that rate was determined. Medtronic attributed the cause of these deaths to user error, not to technical failure of the pump system. However, it should be remembered that human operation is necessary for pump use. Medtronic identified relatively high initial doses (>1 mg/day), opioid naivety, insufficient postoperative patient monitoring, use of concomitant medications, co-morbidities, and dosing calculation errors as factors believed to contribute to death.(84)

Endocrine Effects Reported endocrine effects of long-term opioid therapy include decreased libido, hypogonadism, amenorrhea, and impotence. In a retrospective study of noncancer pain patients treated with a mean daily dose of 4.8 (±3.2) mg for mean of 26.6 (±16.3) months, Abs et al. (2000)(85) found that nearly all men and women had signs of endocrine effects. Twenty-three of 24 men receiving intrathecal opioids had decreased libido or impotency, and most men had decreased serum testosterone, free androgen index, and serum luteinizing hormone (LH). Among the women, 22/32 had decreased libido, 21/21 premenopausal women developed amenorrhea or an irregular menstrual cycle, and 20/21 were not ovulating. Compared with controls, their serum LH, estradiol, and progesterone levels were lower. The authors reported that hormone replacement therapy improved libido in 10/14 men and 7/12 women. In a 12-week prospective study of ten men treated for CNCP with intrathecal opioids conducted by Roberts et al. (2002)(86), serum testosterone, libido, and potency decreased from baseline. The authors proposed that, because LH and follicle-stimulating hormone (FSH) were not reduced, supression of testosterone may occur centrally rather than peripherally (though LH was decreased in women compared with controls in the longer-term study of Abs et al.).

Granuloma: Granulomas at or near the distal tip of intrathecal catheters, have been associated with the use of implantable infusion pumps. Granulomas are inflammatory masses that can be extremely painful and interfere with pump systems' delivery of medication. In a letter to healthcare professionals issued in January 2008, Medtronic reported an incidence of 0.49% for this complication.(50) This figure is estimated for all patients with an intrathecal catheter, including those treated for spasticity or cancer pain. Medtronic acknowledges the actual incidence may be higher due to underreporting, and notes that the cause of these inflammatory masses is poorly understood though high doses or concentrations of opioids may be to blame. Medtronic notes that this rate is rising, possibly due to the increase in duration of pump therapy in individual patients. The total number of patients who have received the implant was not reported. Improved reporting and improved recognition of granuloma may also contribute to this increase. To avoid this complication, Medtronic recommends the administration of intrathecal opioids at the lowest possible effective dose and concentration. Medtronic also recommends vigilant observation of patients at risk for granuloma.(50)

Catheter Connection Failures

In June 2008, Medtronic issued safety alerts to healthcare professionals(87) and inventory and risk managers(87) regarding proper connection of sutureless connector (SC) intrathecal catheters pertinent to catheter models 8709SC, 8731SC, 8596SC, and 8578. The letter to healthcare professionals states that 23 reports (representing 0.15% of total SC implants worldwide) of complications have been attributed to occlusion between the sutureless pump connector and the catheter pump, and another 34 reports (representing 0.22% of total SC implants worldwide) of disconnection of the sutureless pump connector from the catheter port. Medtronic attributes these complications to "improper attachment of the catheter to

the pump" and has issued recommendations for implant techniques(88) and patency verification.(89) Medtronic reports that consequences of sutureless pump connector occlusion and sutureless pump connector disconnection from the catheter pump may include lack of therapeutic effect, return of underlying symptoms and/or withdrawal symptoms, and a clinically significant or fatal drug underdose.(87) Fatal underdoses and severe withdrawal symptoms pertain primarily to patients using an implantable infusion pump to administer baclofen for spasticity, while lack of therapeutic effect and withdrawal symptoms can be expected in patients using the pump to administer pain-relieving drugs for chronic pain.(90) When occlusion of disconnection is identified, the SC catheter must be replaced, entailing surgical correction.(87)

Key Question 3. Is there any evidence of differential efficacy or safety issues amongst special populations?

No conclusions can be drawn regarding differential efficacy or safety of implantable infusion pumps among different patient populations due to an absence of evidence.

To address this key question, we examined the clinical literature included for all of the other key questions and considered the findings of the meta-regressions and subgroup analyses conducted in Key Question 1. We conducted meta-regression on pain scores by underlying cause of pain, and a subgroup analysis of patients with FBSS, but neither of these efforts suggested that pain reduction is associated with underlying cause of pain. Due to the limited reporting on patient characteristics, thorough investigation was not possible, and we did not find any evidence regarding differential efficacy or harms among different populations.

No mentions of differential efficacy or harms were identified in any of the literature considered in the other key questions. As part of our investigation of heterogeneity in pain outcomes in Key Question 1, we conducted meta-regression using primary cause of pain as a covariate. No significant relationship was detected, however, the small size of the evidence base (nine studies reported usable continuous pain scores) may have limited the power of the analysis to detect an effect.

Key Question 4. What are the cost implications and cost effectiveness for implantable infusion pumps?

The available evidence is insufficient to determine whether the long-term costs of implantable infusion pumps are different from the long-term costs of non-pump treatment in the management of chronic non-cancer pain.

This question involves cost-related outcomes such as cost per year of use (including equipment, replacement, and drug cost), comparative costs of non-pump treatment (including oral or transdermal opioids), and cost per quality-adjusted life year.

Implantable infusion pump use incurs a complicated array of costs. Patients are screened before implantation to maximize the likelihood that the drug delivery method will reduce pain without unacceptable side effects. If the trial is successful, further costs involve the delivery system (pump, catheter, and programmer if the system is programmable) and implantation procedure (physician and hospital fees). Post-implantation complications also incur costs; these depend on the type and severity of complication. Ongoing maintenance is necessary to permit refills, dose adjustments, specialist consultations, and any adjunctive medications or treatments. Programmable pumps will need replacement after about five years, which incurs costs for explantation, and purchase/implantation of the new system.

Evidence Base

We retrieved 12 articles for possible inclusion in the evidence base for this Key Question. Nine of these were excluded for reasons listed in Table 29 of Appendix A.

Below, we discuss the three included articles identified by searches. These cost analyses are discussed one at a time, rather than jointly, because their analytic goals and assumptions differed greatly. Two articles described five-year cost analyses of implantable infusion pump treatment for failed back surgery syndrome: one was a cost-effectiveness study in the U.S. in 1997 that used data from the literature and an expert panel,(9) and the second was an actual cost study in Canada in 2000.(10) The third included article was a six-month randomized trial comparing different methods for selecting patients for implantable infusion pumps (a screening trial with intrathecal injection vs. a screening trial with epidural infusion).(11)

We also included a fourth unpublished analysis(12) that was provided to us by the Washington State Health Technology Assessment Program. This was an analysis commissioned by Medtronic, Inc. (the manufacturer of SynchroMed® infusion systems) and prepared by Reden & Anders (an actuarial firm in Eden Prairie, Minnesota). This report estimated the budgetary impact of covering intrathecal drug delivery systems on the Medical Aid Budget of the Washington State Department of Labor and Industries.

Economic Model of Five-year Pump Treatment for Failed Back Syndrome

A cost-effectiveness analysis conducted by de Lissovoy et al. (1997)(9) compared five-year treatment with an implantable infusion pump to five-year treatment with medical management for failed back syndrome. Authors performed their analysis assuming the perspective of a third party payer, and the analysis was funded by a contract between Medtronic, Inc. (Minneapolis, MN) and Battelle Memorial Institute (Washington, DC). Their model entailed numerous assumptions about associated costs, probabilities of different events occurring, and the effectiveness of treatment. These assumptions, which formed the "base case" model, were based on the consensus of an expert panel as well as published data. Authors also explored alternate sets of assumptions under a "worst-case scenario" (entailing larger costs for pump treatment and higher rates of adverse events) as well as a "best-case scenario" (entailing lower costs for pump treatment and lower rates of adverse events). The latter two scenarios served as boundaries for reasonable estimates of the cost-effectiveness of pump treatment. Costs in 2008 are likely different

than those assumed by these authors (who published their work in 1997), but this may be true for both pump use and non-pump treatment. Thus, the *comparative* cost information in the model may still be relevant.

The assumed costs of pump use are listed in Table 15. These represent many different components of the cost of care. Authors also assumed that the annual rate of pump failure increased with time. Specifically, the base-case model assumed that none of the pumps would fail in the first year, 4% of the pumps would fail within the first two years, 12% would fail within the first three years, 32% would fail within the first four years, and 75% would fail within five years (see the de Lissovoy article [Figure 2 on page 101] for more details on assumed failure curves). Further, some patients may elect for device removal without replacement; authors assumed that such patients would incur the removal cost, and subsequent costs for their care would be the same as for medical management. The assumed probabilities, along with those for postsurgical complications and long-term complications, are listed in Table 16.

Given the assumptions about costs and probabilities, authors calculated that the annual cost over five years of pump treatment was $16,579 for the base case analysis (Table 17) (in 1997 U.S. dollars). This compared favorably with an annual cost for medical management of $18,883 (statistical test not reported). Under worst-case assumptions about pump costs, the annual cost was $25,020; under best-base assumptions it was $10,694.We note that under the worst-case assumptions, the cost of pump treatment was higher than the cost of medical management.

For the accumulated costs over five years, authors found that cost was lower in the first year for non-pump therapy, but after all subsequent years the cost was lower for pump in the base-case analysis (Table 18). These five-year estimates were for 1997-2001. Based on 3% annual inflation, the total costs translate in 2008-2012 to $117,917 for non-pump therapy and $114,743 for pump therapy. The time at which accumulated costs for pump (base case) and medical management were equal (i.e., the crossover) was 1.8 years. This crossover time is when the greater upfront costs of the pump are eventually offset by the greater long-term costs of non-pump treatment.

Translating these results to cost-effectiveness, de Lissovoy computed the cost per year of pain relief for implantable infusion pumps vs. non-pump therapy. This cost was estimated to be $624 lower for implantable infusion pumps than for non-pump therapy. In the best-case scenario it was $7,832 lower, and in the worst case scenario, it was $12,276 greater (see Table VII. on page 109 of de Lissovoy et al. 1997 article).(9) These calculations assumed that during the five years after pump implantation, patients would experience 3.65 years with good/excellent pain relief in the base case, 4.05 years in the best case, and 3.25 years in the worst case.

Table 15. Cost Assumptions in the de Lissovoy Model(9)

Type of Cost	Base-case Assumed Cost	Best-case Sensitivity Analysis	Worst-case Sensitivity Analysis
Fees for screening evaluation	$1,213	$788	$1,637
Initial implant charges and fees	$22,495	$14,622	$30,368
Fees for treating minor complications	$255	$166	$344
Charges and fees for treating major complications	$5,044	$3,279	$6,809
Charges and fees for ongoing therapy (including pump refill and supplemental medications)	$380	$250	$520
Charges and fees for pump replacement	$15,897	$10,333	$21,461
Changes and fees for pump explantation (without replacement)	$7,287	$4,737	$9,837

Note: All costs in this table are in 1997 U.S. dollars.

Table 16. Probability Assumptions in the de Lissovoy Model(9)

Type of Event	Base-case Assumed Probability	Best-case Sensitivity Analysis	Worst-case Sensitivity Analysis
Minor postsurgical complication	37.0%	5.4%	44.0%
Major postsurgical complication	2.7%	1.4%	5.4%
Minor long-term complication	8.7%	4.4%	17.4%
Major long-term complication	7.2%	4.5%	11.8%
Decision to discontinue pump use	3.1%	1.6%	6.2%

NOTE: Authors also assumed an increasing rate of pump failure over the five-year period. The base-case model assumed that none of the pumps would fail in the first year, 4% of the pumps would fail within the first two years, 12% would failure within the first 3 years, 32% would fail within the first four years, and 75% would fail within five years (see the de Lissovoy article [Figure 2 on page 101] for more details on assumed failure curves).

Table 17. Estimated Annual Overall Costs from the de Lissovoy Model(9)

		Assumed Adverse Event Rates		
		Best-case	Base-case	Worst-case
Assumed Component Costs	Best-case	$10,694	$10,862	$12,164
	Base-case	$16,386	$16,579	$18,277
	Worst-case	$22,217	$22,565	$25,020

NOTE: All costs in this table are in 1997 U.S. dollars. For comparison, authors estimated that the annual cost of medical management (i.e., not using an implantable infusion pump) was $18,883. For the total accumulated costs over five years for all four analyses, see Table 18.

Table 18. Total Accumulated Costs Over Five Years from the de Lissovoy Model(9)

Total *Accumulated* Cost at end of:	Medical Management	Pump: Base-case Analysis	Pump: Best-case Analysis	Pump: Worst-case Analysis
Year One	$18,883	$23,998	$17,199	$39,580
Year Two	$36,843	$35,256	$22,247	$51,627
Year Three	$53,881	$46,649	$27,496	$65,708
Year Four	$69,995	$60,647	$35,751	$84,483
Year Five	$85,186	$82,893	$53,468	$125,102

NOTE: All costs in this table are in 1997 U.S. dollars. Numbers were estimated by ECRI Institute based on Figure 3 on page 106 of de Lissovoy et al. (1997) article.(9) Shaded cells indicate the option with lower accumulated cost when comparing medical management to the base case analysis. Authors used 5% time discounting in all analyses.

Actual Analysis of Five-year Pump Treatment for Failed Back Syndrome

This small study (Kumar et al. (2002)(10)) was conducted in Canada, and health care system differences make its results less applicable to the U.S. Authors examined actual cost data over five years in the use of pump treatment. The authors examined data on 88 patients with chronic pain due to failed back syndrome. These patients were originally in a group of 400 that was screened for spinal cord stimulation therapy; the 88 included patients did not achieve sufficient pain relief to proceed with stimulation therapy They were randomized into two groups of 44 patients each: one group was screened for suitability for an implantable infusion pump, whereas the other group received conventional pain therapy. During the pre-implantation screening, only 23/44 patients in the pump group responded favorably to intrathecal morphine, and remained in the trial, whereas the 21 nonresponders were then excluded. Therefore, the analysis compared a) the ***cost of intrathecal administration among those who had a successful screening trial (N = 23)*** vs. b) the ***cost of conventional pain therapy among those who did not undergo a screening trial (N = 44)***. The authors did not report any cost information for the 21 nonresponders originally assigned to the pump group, which would have been helpful information about treating this sub-population.

The authors of this analysis acknowledged that this design was not scientifically optimal:

> "Ideally, groups would have been composed of patients who had been referred for an IDT [intrathecal drug therapy] trial and who responded favorably to a trial infusion and were *then* [italics added] randomly assigned to either Group A or Group B. Patients in Group A would have continued to receive the selected drug therapy through the implantable pump, whereas patients in Group B would have their pumps explanted or would have received an infusion of saline as a placebo. In that event, patients in the control group would have undergone a surgical procedure specifically designed not to benefit the patient, an ethically and morally unacceptable situation."(10) (page 804)

The hypothesized design would have eliminated the problem of selecting patients for response in one group but not the other. Some patients may be hard-to-treat *in general*, regardless of treatments attempted. Excluding such patients from one group, but leaving them in the other group, introduces a bias in favor of the first group. Above, the authors argued that an explanted pump (or a sham pump) would have been unethical. This may be true, but the point remains that differential exclusion of nonresponders makes it more difficult to interpret the study results. Authors also did not report comparative baseline characteristics of the two measured groups of patients, which would have permitted an assessment of the integrity of the comparison. Other design problems include the lack of blinding, and concealment of allocation. The study did not report the funding source, but authors stated that they have "no financial interest in the subject under discussion." With these important caveats in mind, we proceed to the results.

For the 23 patients who received the implantable infusion pump, the average per-patient five-year cost was $43,508 USD (converted by ECRI Institute from the reported $29,410 CAD using a 2000 exchange rate U.S./Canada of 0.6760 from http://www.bankofcanada.ca for June 30, 2000). This total comprises $23,270 of initial evaluation and implantation costs (listed in Table 19) and $20,328 of five-year maintenance costs (listed in Table 20).

Authors also performed best-case and worst-case analyses. The best-case analysis that was restricted to the nine patients who did not have any complications during the five-year period; their average five-year accumulated cost of implantable infusion pump use was $41,811. The other 14 patients all experienced at least one complication, and they comprised the worst-case analysis; their average five-year accumulated cost of implantable infusion pump use was $46,052. These extremes differed by $4,241; this difference was mostly explained by costs during the first year after implantation ($3,722, or 88% of the difference).

By comparison, the average five-year cost of conventional pain management (CPT) among the 44 patients who received this strategy was $56,257 USD. This was statistically significantly higher than the average five-year cost of implantable infusion pump use ($p = 0.028$). A breakdown of the component costs appears in Table 21. Interestingly, oral pharmacotherapy agents themselves only accounted for $6,368

(11% of the total). Larger components included the costs of thrice-yearly hospital stays for breakthrough pain ($13,913 or 25% of the total) and physiotherapy (occurring about once a week on average, and accruing $12,781 or 23% of the total).

What explains the greater five-year cost in conventional pain management as compared to implantable infusion pump use? One possible answer is the greater need for supplemental treatments, which includes hospital admissions and ER visits for breakthrough pain, as well as adjunctive therapies such as physical therapy (see Table 20 and Table 21). In the implantable infusion pump group, no patient required such interventions. By contrast, in the conventional pain management group, an average of $35,266 was required for these purposes, representing 63% of the five-year cost. However, recall that the conventional group was not prescreened for response to intrathecal administration. Based on the reported data, one cannot determine the cost of conventional pain management specifically among patients who would have responded to intrathecal administration.

As with the de Lissovoy analysis, Kumar presented accumulated costs over the five year period (Table 22). Initially, costs of pump treatment are higher, but at 2.3 years after implantation, costs became greater with conventional pain management. Authors also performed sensitivity analyses of this crossover point:

- If the cost of the implantable infusion pump itself were increased by 50%, then the crossover point would occur at 2.8 years.
- If the life expectancy of the pump were increased by 50%, then the crossover point would not change because the initial pump costs would still predominate
- If complication-associated costs were decreased by 50%, the crossover point would occur at 2.2 years.

Kumar also compared rates of disability and return to work. As measured by the Oswestry Disability Index (ODI), the average five-year improvement among those who received the pump was 27%, whereas the other group improved an average of 12% (statistical test not reported or calculable from reported data). For return to work, authors stated that in the pump group “two patients who had been working with intermittent time loss prior to implantation continue to work with increased comfort and without any disruptions.” Also, two additional patients in that group “were unemployed before undergoing implantation and have been able to take up part time employment”. By contrast, in the non-pump group, no patients returned to work during the five-year study period.

Table 19. Initial Evaluation and Implantation Costs of Implantable Infusion Pump Use in the Kumar Analysis(10)

Cost category	Cost per Unit	Number of Units	Total Cost
Professional fees: Psychiatrist	$160	1	$160
Professional fees: Social worker	$124	1	$124
Professional fees: General practitioner	$65	1	$65
Professional fees: Neurosurgeon	$84	1	$84
Professional fees: Neurologist	$126	1	$126
Professional fees: Orthopedic surgeon	$71	1	$71
Diagnostic imaging: CT scanning	$688	1	$688
Diagnostic imaging: MR imaging	$1,546	1	$1,546
Diagnostic imaging: Radiography	$53	2	$107
Diagnostic imaging: Myelography	$200	1	$200
Surgical costs: Anesthesia	$284	1	$284
Surgical costs: Neurosurgical professional fees	$877	1	$877
Surgical costs: Assistant surgeon	$92	1	$92
Equipment: Synchromed pump	$10,487	1	$10,487
Equipment: Intrathecal drugs	$65	4	$260
Hospital admission for implantation	$928	6.24	$5,788
Complications: Infection: cost of antibiotics	$932	0.24	$224
Complications: Flipping pump: cost of surgery	$544	0.24	$131
Complications: Leaky/broken/slipped catheter: cost of neurosurgeon/anesthesiologist	$544	0.29	$158
Complications: Leaky/broken/slipped catheter: cost of new catheter	$814	0.29	$236
Complications: Replacement of explanted pump, including professional fees	$12,433	0.04	$497
Complications: Hospital stay for treatment	$928	1.15	$1,067
Total			**$23,270**

[a] The table shows 2000 USD, even though the study cited figures in 2000 CAD; ECRI Institute performed the conversion using a 2000 exchange rate U.S./Canada of 0.6760 (from http://www.bankofcanada.ca for June 30, 2000).

Table 20. Five-year Implantable Infusion Pump Maintenance Costs from the Kumar Analysis(10)

Cost category	Cost per Unit	Number of Units	Total Cost
Physician contacts: Family physician	$65	20	$1,302
Physician contacts: Neurosurgeon	$84	10	$843
Nurse contact: Dose optimization	$44	57.2	$2,538
Pharmacotherapy: Pain flare-ups	$447	5	$2,234
Pharmacotherapy: Increasing doses for refills	$178	5	$888
Hospital admission for breakthrough pain	$928	0	$0
Adjunctive therapies: Physiotherapy	$44	0	$0
Adjunctive therapies: Massage therapy	$59	0	$0
Adjunctive therapies: Chiropractic therapy	$33	0	$0
Adjunctive therapies: Acupuncture	$52	0	$0
Pump replacement during Year 5: Pump	$10,487	1	$10,487
Pump replacement during Year 5: Anesthesia	$138	1	$138
Pump replacement during Year 5: Neurosurgeon	$299	1	$299
Pump replacement during Year 5: General practitioner consult	$407	1	$407
Pump replacement during Year 5: Neurosurgeon	$84	1	$84
Pump replacement during Year 5: Consult	$92	1	$92
Pump replacement during Year 5: Hospital stay	$928	1	$928
Total			**$20,238**

[a] The table shows 2000 USD, even though the study cited figures in 2000 CAD; ECRI Institute performed the conversion using a 2000 exchange rate U.S./Canada of 0.6760 (from http://www.bankofcanada.ca for June 30, 2000).

Table 21. Five-year Costs of Conventional Pain Management from the Kumar Analysis(10)

Cost category	Cost per Unit	Number of Units	Total Cost
Professional fees: General practitioner	$33	120	$3,905
Professional fees: Neurologist	$126	5	$629
Professional fees: Neurosurgeon	$84	5	$422
Professional fees: Orthopedic surgeon	$71	5	$355
Professional fees: Psychiatrist	$160	5	$799
Professional fees: Social worker	$31	20	$621
Hospital admission for breakthrough pain	$928	15	$13,913
Pharmacotherapy	$1,274	5	$6,368
Adjunctive therapies: Physiotherapy	$44	288	$12,781
Adjunctive therapies: Massage therapy	$59	50.5	$2,988
Adjunctive therapies: Chiropractic therapy	$33	85.9	$2,796
Adjunctive therapies: Acupuncture	$52	53.85	$2,788
Initial Diagnostic imaging: CT scanning	$688	1.8	$1,238
Initial Diagnostic imaging: MR imaging	$1,546	1	$1,546
Initial Diagnostic imaging: Radiography	$53	6.78	$361
Initial Diagnostic imaging: Myelography	$200	1.4	$280
Diagnostic precipitated by flare-ups: CT and MR imaging of lumbar spine	$2,234	2	$4,467
Total			**$56,257**

Note: All costs in this table are in 2000 U.S. dollars.

Table 22. Total Accumulated Costs Over Five Years from the Kumar Analysis(10)

Total *Accumulated* Cost at end of:	Conventional Pain Management	Pump: Base-case Analysis	Pump: Best-case Analysis	Pump: Worst-case Analysis
Year One	$13,089	$24,830	$23,654	$27,376
Year Two	$22,753	$26,391	$25,214	$28,936
Year Three	$34,651	$27,951	$26,775	$30,497
Year Four	$44,315	$29,512	$28,336	$32,058
Year Five	$56,257	$43,508	$41,811	$46,052

NOTE: All costs in this table are in 2000 U.S. dollars. Numbers were estimated by ECRI Institute based on Figure 1 on page 807 of Kumar (2000) article.(10) In this analysis, the "best case" was simply the costs of the nine patients who did not have any complications during five years, whereas the "worst case" was simply the costs of the 14 patients who had at least one complication. Shaded cells indicate the option with lower accumulated cost when comparing conventional pain management to the base case analysis.

Six-month Randomized Trial

In a small trial, Anderson (2003)(11) reported cost data in failed back surgery syndrome patients who were screened for an implantable infusion pump (study funding by Medtronic, Inc.). Authors compared the cost of screening with intrathecal injection (18 patients) vs. screening with epidural infusion (19 patients). Twelve of the 18 screened using intrathecal injection (67%) reported at least 50% pain relief on two consecutive ratings, and subsequently received an implantable infusion pump. The other six patients did not receive a pump; authors did not report what treatment they did receive. Fifteen of the 19 screened using epidural infusion (79%) reported at least 50% pain relief on two consecutive ratings, and subsequently received an implantable infusion pump. Treatment was not reported for the other four patients. At baseline, the two groups were statistically similar with respect to age (mid 50's), number of prior surgeries (2-3), gender distribution (about 50/50), pain duration (about two-thirds of patients had 5+ years pain duration), degree of pain as measured by VAS (about 80 on a 0-100 scale), and Medication Quantification Scale (scores of 26-28).

The reported cost data appear in Table 23. Screening with intrathecal injection was much less expensive ($1,862 in 2003 U.S. dollars) than screening using epidural infusion ($4,762) (statistical p value <0.0001). The cost of the pump and implanting it was approximately $20,000. Authors also noted that the screening trial took significantly shorter with intrathecal injection (median one day) than epidural infusion (median two days). The hospital stay itself was also shorter in the intrathecal injection group (see table). This may have been partially due to the need for catheter placement in the OR for the epidural infusion group; whereas no OR visits occurred in the intrathecal injection group. The two groups did not differ on other reported costs such as clinical visits, physician visits, or visits to other healthcare professionals. No other cost data were reported.

Table 23. Reported Cost Data in the Six-month RCT of Anderson(11)

Type of Cost	Screened Using *Intrathecal* Injection (N = 18; 12 of whom later received the pump)	Screened Using E*pidural* Infusion (N = 17; 13 of whom later received the pump)	Reported p value[a]
Screening trial	$1,862 (95% CI: $1,590 to $2,134) (N = 18)	$4,762 (95% CI: $4,501 to $5,023) (N = 17)	<0.0001
Pump system implantation	$19,599 ($17,684 to $21,514) (N = 12)	$20,069 ($18,252 to $21,886) (N = 13)	0.65
Duration of screening trial (days)	1 (IQR 1 to 2)	2 (IQR 2 to 2)	<0.0001
Length of hospital stay	Median 3 days	Not reported	Not reported, but the intrathecal group had significantly shorter stay.
Number of clinical visits during six months	6 (IQR 5 to 11)	7 (IQR 5 to 11)	0.70
Number of other physician visits during six months	0 (IQR 0 to 1)	1 (IQR 0 to 2)	0.50
Number of visits to other healthcare professionals during six months	0 (IQR 0 to 1)	0 (IQR 0 to 0)	0.48

95% CIs calculated by ECRI Institute.
Shaded cells indicate statistically significant difference between screening methods

IQR Interquartile range (the difference between the 25th percentile and the 75% percentile)

[a] The statistical test was analysis of variance for the first two rows, and the Wilcoxon test for the other rows.

Reden & Anders Analysis

This analysis(12) estimated the budgetary impact of covering intrathecal drug delivery systems on the Medical Aid Budget of the Washington State Department of Labor and Industries (the analysis also considered spinal cord stimulation, but that is outside the scope of this report). Because the report directly analyzed the cost impact of implantable infusion pumps on the Washington State L&I budget, its results will be of particular interest to readers of this review. As a caveat, however, readers should be aware that the report was commissioned by Medtronic, Inc., the manufacturer of SynchroMed® infusion systems. The analysis itself was conducted by an independent party (Reden & Anders), which may reduce concerns about bias, but the financial interest of the funding source must nevertheless be taken into account when considering the findings.

Reden & Anders(12) utilized insurance claims data from 1,647 patients who had received intrathecal drug delivery systems within a 3.5 year period (January 2003 to July 2006). The data resided in an administrative claims database owned by Ingenix, Inc. Authors did not report the medical diagnoses of these patients, so the data likely included patients who had cancer or spasticity as their primary diagnosis as well as patients with chronic noncancer pain. The total of billed charges for these patients was approximately $49M; these charges included not only device and implantation costs, but also medical and prescription drug costs. There was no explicit mention of adverse event costs in the Reden & Anders analysis, but presumably these costs were included because the claims were said to include "the entire longitudinal claims histories" within the 3.5 year timeframe. The cost of early pump replacement was included because some patients had pertinent insurance claims during the 3.5 year timeframe. Later pump replacement (e.g, after 3.5 years) was incorporated into their model by assuming replacement every seven years (see below for further discussion of this point).

Even though all patients received intrathecal drug delivery devices, the authors attempted to estimate the hypothetical costs of treating these patients if they had *not* received the devices. This estimate was based on the medical claims data from the same patients in the *month prior to implant*. The reasonableness of this approach depends completely on whether that month's cost (an average of $4,055) is predictive of future non-device medical costs of these patients. For comparison, the models of de Lissovoy and Kumar employed far lower estimates of the monthly cost of non-pump treatment: $1,420 by de Lissovoy and $920 by Kumar). The markedly higher estimate in the Reden and Anders analysis may be due to the inclusion of other types of patients (e.g., cancer patients), or its focus on the single month before implantation.

Another key issue was whether any long-term cost savings might be realized after implantation of the system. One set of analyses (referred to as "Method 1") assumed *no* ongoing cost savings from implantation (i.e., that there would be no decrease in the amount of prescription drugs necessary, or physician visits, etc.). Another set of analyses (referred to as "Method 2") assumed that such savings would occur. The amount of savings was estimated "as demonstrated by the R&A research data for those individuals receiving the implant" (page 10; no further explanation provided).

The analysis was specifically tailored to Washington State L&I by using that department's fee schedules for the relevant CPT codes or revenue for July 1, 2006. This translation was possible in most cases, but when it was not, Reden & Anders assumed reimbursement "at a percentage of billed charges" (actual percentage not reported).

Authors projected comparative costs of no-implantation vs. implantation to 30 years after implantation. Authors assumed that every seven years, each patient would require a new device (i.e., reimplantation). This is less frequently than assumed by the de Lissovoy and Kumar analyses (approximately every four years). To support the assumption of seven years, Reden & Anders stated that:

> "Historically, the average operating life of the SCS/IDD device was about 3 to 5 years. However, today the device's lifetime averages from 7 to 9 years. We believe a 7-year device lifetime may be conservative, but it is a reasonable estimate for the purpose of this study." (page 11)

Authors performed two sensitivity analyses of this assumption, one with replacement at five years and another at nine years (these are included in our summary of results below). Also, because costs generally increase over time, three trend assumptions were made for the 30-year projections: 1) a 13% annual billed charge trend; 2) annual net medical trend rates of 10% for year 1, 9% for year 2, 8% for year 3, 6.5% for year 4, 5% for year 5, and 4% for years 6 through 30; and 3) a 3% annual discount rate.

A summary of the report's 30-year projections appears in Table 24 below. Authors also performed three types of sensitivity analyses; these results appear in Table 25 below. These analyses considered alternate assumptions about the timing of reimplantation, the net medical annual trend, and the annual discount rate.

To address the impact of covering intrathecal drug delivery systems on the Washington State L&I budget, authors provided estimates for the first six years after implantation. These analyses assumed that each year would involve 72 new implantations of intrathecal drug delivery systems (this assumption was "based on a blend of WA's current experience and the SCS/IDD coverage experience of five similar states" (page 22); no further details were provided). They also assumed that no implants are currently covered. Under Method 1 (which assumed no cost savings from the implant), the total annual cost was $1,789,679 (0.34% of the assumed $527M total budget of Washington L&I). Under Method 2 (which assumed cost savings from the implant), the first year was estimated to cost $879,695, and the subsequent five years were estimated to realize savings ranging from approximately $1M in year 2 to approximately $8M in year 6 (ranging from 0.17% to 1.52% of the total budget). Authors also estimated, using Method 2, the time to cost neutrality was 18 months (they did not perform this analysis under Method 1).

Table 24. Base-Case Findings of the Reden & Anders analysis(12)

Base Case Findings				
Method 1 (assumes that there *would be NO cost savings* from the implantation)				
	Base Cost, No Implant	**Including Implant**	**Additional Costs[a]**	**Additional Costs per Year[a]**
Month of implant	$4,055	$28,446	$24,391	$24,391
1 Year Post Implant	$54,877	$81,299	$26,422	$26,422
3 Years Post Implant	$165,679	$192,102	$26,423	$8,808
5 Years Post Implant	$285,395	$311,818	$26,423	$6,606
10 Years Post Implant	$598,399	$658,537	$60,138	$6,014
15 Years Post Implant	$926,232	$1,022,343	$96,111	$6,407
20 Years Post Implant	$1,269,598	$1,365,709	$96,111	$4,806
30 Years Post Implant	$2,005,905	$2,181,348	$175,443	$5,848
Method 2 (assumes that there *would be cost savings* from the implantation)				
	Base Cost, No Implant	**Including Implant**	**Additional Costs[a]**	**Additional Costs per Year[a]**
Month of implant	$4,055	$27,230	$23,175	$23,175
1 Year Post Implant	$54,877	$67,267	$12,390	$12,390
3 Years Post Implant	$165,679	$127,606	- $38,073	- $12,691
5 Years Post Implant	$285,395	$186,442	- $98,953	- $24,738
10 Years Post Implant	$598,399	$457,758	- $140,641	- $14,064
15 Years Post Implant	$926,232	$735,133	- $191,099	- $12,740
20 Years Post Implant	$1,269,598	$932,083	- $337,515	- $16,876
30 Years Post Implant	$2,005,905	$1,542,581	- $463,324	- $15,444

NOTE: All of the above calculations used a 3% annual discount rate ("present-valued").

[a] The "Additional Costs" column is the difference between the cost without an implanted pump and the cost with an implanted pump. A negative number reflects estimated savings from the pump.

Table 25. Sensitivity Analyses of the Reden & Anders Analysis(12)

Sensitivity Analysis #1: Timing of Reimplantation			
Assumption	Base case: 7 years	9 years	5 years
Method 1 (assumed *no cost savings*): 30 Years Post Implant Average additional costs per Year[a]	$5,808	$4,582	$19,026
Method 2 (assumed *cost savings*): 30 Years Post Implant Average additional costs per Year[a]	- $15,444	- $15,012	- $7,485
Sensitivity Analysis #2: Net Medical Annual Trend Rate			
Assumption	Base case: 10% year 1 9% year 2 8% year 3 6.5% year 4 5% year 5 4% yrs 6-30	+1% from base case	-1% from base case
Method 1 (assumed *no cost savings*): 30 Years Post Implant Average additional costs per Year[a]	$5,808	$6,766	$5,061
Method 2 (assumed *cost savings*): 30 Years Post Implant Average additional costs per Year[a]	- $15,444	- $18,148	- $13,281
Sensitivity Analysis #3: Annual Discount Rate			
Assumption	Base case: 3%	+1% from base case	-1% from base case
Method 1 (assumed *no cost savings*): 30 Years Post Implant Average additional costs per Year[a]	$5,808	$5,001	$6,808
Method 2 (assumed *cost savings*): 30 Years Post Implant Average additional costs per Year[a]	- $15,444	- $13,316	- $18,035

[a] A negative number reflects estimated savings.

Cost Overview

Below, we provide a tabular summary of the three long-term cost analyses (Table 26). In general, we deemed the evidence insufficient to determine whether long-term costs of implantable infusion pump treatment are different from those of non-pump treatment. Our reasons for this determination are described next.

The de Lissovoy analysis(9) was conducted at least 11 years ago using simulated patients within a deterministic Markov model, and more advanced methods are now available for more accurate cost analysis. Authors did incorporate many important costs, including pump replacement and adverse events, and the estimated five-year total costs for the two treatments were very similar ($82,893 for the pump vs. $85,186 for non-pump). However, sensitivity analyses revealed very wide ranges for pump treatment (from $53,468 to $125,102). This wide range of uncertainty casts doubt on any conclusion about comparative long-term costs.

The Kumar analysis(10) was conducted in Canada eight years ago. Canadian costs structures are quite different from those in the US. Also, interpretation of the study results was complicated by the differential selection of patients in one group but not the other, which may have biased the study to find lower costs in the pump group. These two issues meant that we did not draw conclusions based on its results.

The other two analyses were also judged inconclusive for long-term comparative costs for chronic non-cancer pain. The Anderson trial(11) focused on the costs of different screening methods for the pump, rather than costs of pump vs. non-pump treatment. The Reden and Anders analysis may have included patients without chronic non-cancer pain, so its precise relevance is unknown. Also, authors attempted to estimate the cost of non-pump treatment using costs incurred in the single month prior to pump implantation. This latter cost (about $4,000 per month) was much higher than the costs reported in the other analyses (about $1,000 per month), calling into question any comparison with pump treatment costs.

Table 26. Overview of the Three Long-term Cost Analyses

Cost Analysis	Primary Methods	Primary Results
De Lissovoy et al. (1997)(9) **Country**: USA **Type**: CEA model **Timeframe**: 5 yrs	**Patients**: Chronic pain due to FBSS. **Comparison**: Pump vs. non-pump **Data source(s)**: Expert opinion and the published literature **Assumptions**: Initial implant and fees $22,495; pump replacement $15,897; (other costs also; see tables in main text). Major postsurgical complication rate of 2.7%; major long-term complication rate of 7.2%. Pump failure rate increasing from 0% in the first year to 75% within five years. Elective removal of the pump in 3% of patients annually. For non-pump treatment, annual charge of $4,847 for medications, and $5,634 for hospital admissions for uncontrolled pain (other costs also; see tables in main text). 5% annual discount rate. For pain relief, the typical pump patient would have 3.65 of the five years with good/excellent pain relief, whereas the typical non-pump patient would have no years with good/excellent pain relief. **Sensitivity analyses**: Best-case analysis assumed lower adverse event rates and lower costs of pump treatment; worst-case analysis assumed the opposite. **Funding source**: A contract between Medtronic Inc. and the Battelle Memorial Institute	**Base case.** Total five-year cost of pump treatment was $82,893 in 1997 dollars. For non-pump treatment it was $85,186 (statistical test not reported). **Best case**: Total five-year cost of pump treatment $53,468 in 1997 dollars. **Worst case:** Total five-year cost of pump treatment $125,102 in 1997 dollars. **Estimated time to cost neutrality for the base case:** 1.8 years.
Kumar et al. (2002)(10) **Country**: Canada **Type**: Cost outcomes in an RCT **Timeframe**: 5 yrs	**Patients**: Chronic pain due to FBSS. **Comparison**: Pump (N = 23) vs. non-pump (N = 44). Pump patients had first responded favorably to a screen with intrathecal morphine, but no such selection occurred in the non-pump group. **Data source(s)**: Actual costs incurred; fee schedules from Saskatchewan; pump list price for Canada; pharmacotherapy costs according to the Saskatchewan Health Formulary **Assumptions**: That the differential screening of patients would not bias the results. Initial pump implantation and fees $23,270. All pumps replaced after four years. For the pump group, no hospital admissions for breakthrough pain, and no adjunctive therapies necessary (except for pharmacotherapy for pain flare-ups and pump refills) (other costs also; see main text). For the non-pump group, 15 annual hospital admissions for breakthrough pain, and adjunctive therapies necessary (other costs also; see main text). **Sensitivity analyses**: Best-case analysis was restricted to the 9 pump patients who did not experience any complications; worst-case analysis was restricted to the 14 pump patients who experienced at least one complication. **Funding source**: Not reported, but authors stated that they have "no financial interest in the	**Base case.** Total five-year cost of pump treatment was $43,508 in 2000 U.S. dollars. For non-pump treatment it was $56,257 (statistical p value 0.028 when compared to pump treatment). **Best case**: Total five-year cost of pump treatment was $41,811 in 2000 U.S. dollars **Worst case:** Total five-year cost of pump treatment was $46,052 in 2000 U.S. dollars **Estimated time to cost neutrality for the base case:** 2.3 years.

Cost Analysis	Primary Methods	Primary Results
	subject under discussion."	
Reden and Anders (2006)(12) **Country**: USA **Type**: Cost model **Timeframe**: 30 yrs	**Patients:** Diagnoses not reported; probably included CNCP and other diagnoses. **Comparison**: Pump vs. non-pump **Data source(s)**: Ingenix Inc.; Washington L&I fee schedules and inpatient and outpatient reimbursement for 7/1/06; pharmacotherapy costs at standard costs plus dispensing fee **Assumptions**: That not receiving the pump would incur the same monthly costs as costs incurred in the single month prior to receiving the pump ($4,055 per month). Pump replacement every 7 years; some incidents of earlier pump replacement did occur and were incorporated. "Method 1" assumed no ongoing cost savings from the pump, whereas "Method 2" assumed savings (see main text). Trend assumptions included 13% annual billed charge trend; annual net medical trends decreasing from 10% for year 1 to 4% for years 6 through 30; 3% annual discount rate. **Sensitivity analyses**: Three types: 1) pump replacement every 5 years, or every 9 years; 2) net annual medical cost trend +1% from base case or -1% from base case; 3) annual discount rate 2% or 4%. **Funding source**: Medtronic, Inc.	**Base case:** Non pump 30-year total cost was $2,005,905 per patient. Pump 30-year total cost using Method 1 (assumed no cost saving from implantation) was $2,181,348 per patient. Pump 30-year total cost using Method 2 (assumed cost saving from implantation) was $1,542,581 per patient. **Sensitivity analysis of timing of pump replacement:** Replacement every 5 years meant an annual pump vs. no-pump difference of $19,026 for Method 1 (favoring non-pump) and -$7,485 for Method 2 (favoring pump). Replacement every 9 years meant an annual pump vs. no-pump difference of $4,582 for Method 1 (favoring non-pump) and -$15,012 for Method 2 (favoring pump). **Other sensitivity analyses**: see main text. **Estimated time to cost neutrality for the base case:** 1.5 years using Method 2 (neutrality analysis not performing using Method 1).

CEA Cost effectiveness analysis
FBSS Failed back surgery syndrome
RCT Randomized controlled trial

Previous Systematic Reviews

Our searches identified four recently published systematic reviews on the use of implantable infusion pumps for CNCP.

While we sought data from studies on any drug delivered by a pump, some of the previous systematic reviews limited their scope to a certain drug or drug class delivered to a certain anatomic location. One assessed the use of intrathecal opioids or ziconotide in ten articles,(91) one assessed the use of intrathecal fentanyl or sufentanil in four studies,(92) one assessed 11 intrathecal studies but did not specify the type of drug used, (84) and one assessed 114 studies of intrathecal opioids for both cancer and noncancer pain.(93) We restricted our review to longer-term efficacy or effectiveness outcomes, i.e., those with at six months of treatment or longer. None of the previous systematic reviews had such criteria and evaluated outcomes at shorter-term time points.

Outcomes of interest both in this report and in previous reports included pain, functioning, quality of life, and harms. The authors of all the previous systematic reviews reported improvements in pain relief, but conclusions were weak because the evidence base consisted of observational studies and because two of the four reviews did not perform quantitative analysis. No conclusions were drawn regarding quality of life in the systematic review that examined quality of life due to the differences among studies. Quantitative methods in previous reviews were less rigorous than those used in this one. No major adverse events were reported.

Two additional systematic reviews were brought to our attention by Medtronic, Inc. and the Washington State Health Care Authority.(94,95) Both of these reviews assessed intrathecal administration, but one covered opioids in general while the other primarily pertained to fentanyl but also covered morphine. These reviews summarized the relevant literature published through their inclusion dates, but neither performed any quantitative synthesis. Both concluded that intrathecal drug therapy was associated with general improvement in pain, but found evidence regarding other outcomes to be sparser.

These systematic reviews are summarized in Table 27 on the next page.

Table 27. Previous Systematic Reviews

Citation	Search Strategy	Key Inclusion Criteria	Evidence Base	Outcomes Assessed	Authors' Conclusions
Identified by ECRI Institute					
Turner et al. 2007(91)	MEDLINE, Cochrane, and others through 10/2005	English language Treatment of pain with opioid or ziconotide intrathecally or by programmable pump Patient diagnosis not limited to spasticity or specific diseases Outcomes on pain, function, or complications reported	10 articles (6 for effectiveness and complications and 4 for complications only)	Pain, functioning, adverse events	Improvements in pain were observed, but authors caution against drawing conclusions because of the weak evidence base (observational studies)
Waara-Wolleat et al. 2006(92)	MEDLINE through 4/15/2005	Studies on intraspinal fentanyl or sufentanil Acute care studies "generally not included"	Intrathecal Fentanyl 3 articles (n = 30) Sufentanil 1 article (n = 22)	Pain, adverse events	"The long-term clinical use of fentanyl or sufentanil is limited to a few studies with relatively small numbers of patients. Overall, the analgesic response to chronic infusion of either opioid was generally favorable and relatively well tolerated."
Simpson et al. 2003(96) for the Royal Australian Safety and Efficacy Register of New Interventional Procedures - Surgical	MEDLINE, PreMEDLINE, EMBASE, PubMed, and Current Contents searched from inception to 4/2003. Internet searched in 2/2003. No language restriction	Intrathecal studies were included RCTs or other controlled or comparative studies and case series and studies were retrieved in searches – criteria for selecting them not reported More complete study included in event of duplication	1 RCT, 6 case series, 3 cost studies	Pain reduction, composite toxicity score, safety, and cost considerations	"Infusion of opioid agents for treatment of chronic pain or baclofen for treatment of spasticity, intrathecally via implantable infusion devices appears effective for patients who have been screened for response to intrathecal medication prior to implantation. This method of treating chronic pain or spasticity appears safe, although drug related complications do occur (similarly with systemic or parenteral drugs) but device related complications (such as catheter related complications) can also occur which may result in surgical revision or removal of the device. Treatment of chronic pain via intrathecal opioids and spasticity via intrathecal baclofen may be less costly than medical management in the long term."

Citation	Search Strategy	Key Inclusion Criteria	Evidence Base	Outcomes Assessed	Authors' Conclusions
Williams et al. 2000(93)	MEDLINE, EMBASE, CancerCD, PubMed searched; years not specified	Studies on intrathecal opioids for chronic pain, including cancer pain	114 studies with over 2,000 patients	Pain, return to work, range of motion, side effects and complications, cost	"No randomised, controlled or comparator data were found while carrying out this review. All information is therefore suboptimal. Published reports frequently use non-standard outcome measures on a heterogenous patient population receiving different types of intrathecal pumps and drugs over varying periods. These variables make analysis very difficult. However, such data as are available indicate a generally positive effect of the therapy, with side effects and complications occuring in about a quarter of recipients, but it is difficult to draw definite conclusions because the quality of the data is so poor. Furthermore, the important treatment question, "Is this therapy any better than existing treatments?" is not answered by this review because of the lack of comparator data. The opinions for UK experts were not of such and overwhelmingly positive nature as the published reports."

Citation	Search Strategy	Key Inclusion Criteria	Evidence Base	Outcomes Assessed	Authors' Conclusions
Provided by Medtronic, Inc. or Washington State Health Care Authority					
Martin 2005(94) for WCB Evidence-based Practice Group	PubMed, Cochrane Library, Bandolier, U.S. Agency for Healthcare Research and Quality, NHS, Web sites of members of International Network of Agencies for Health Technologies	Studies on adult humans with at least abstract in English on intrathecal fentanyl. Reviews were excluded if quality assessment methodology is not apparent.	3 systematic reviews, no controlled trials, 6 case series, 2 surveys or non-systematic reviews, 2 cost-related articles	Studies individually reviewed; assessment not conducted by outcome	"To date there is a paucity of published literature on the effectiveness of intrathecal fentanyl in treating nonmalignant chronic pain patients. Level 4 evidence [case series] did suggest some positive evidence on the effectiveness of intrathecal morphine in treating chronic nonmalignant pain. However, studies also showed that: 1. There was no patient selection criteria that guaranteed a high level of success of the treatment; 2. The use of intrathecal morphine was associated with a high incidence of side effects related to the drug itself, the drug delivery vehicles, and the complications of the surgery; 3. Chronic nonmalignant pain patients treated with intrathecal morphine were usually also prescribed other analgesics, antidepressants, and/or even oral opioids at the same time. 4. The cost effectiveness studies done on intrathecal morphine did not provide definitive evidence on its cost effectiveness due to the paucity of relevant data necessary to construct such a study. Methodological concerns around the one published study on cost effectiveness will likely negate any of its conclusions."

Citation	Search Strategy	Key Inclusion Criteria	Evidence Base	Outcomes Assessed	Authors' Conclusions
Hayes, Inc. 1999(95)	PreMEDLINE, MEDLINE, HEALTHSTAR, EMBASE, and Current Contents databases searched from 1966-9/1999	None reported	12 case series	Pain, "overall health status," safety, drug addiction/tolerance, cost-effectiveness	"There is evidence from case series reports and small, uncontrolled prospective studies that intrathecal opioid therapy via implantable infusion pump can provide effective pain relief for selected patients with chronic nonmalignant pain who do not respond to or cannot tolerate other less invasive pain control measures, who have a life expectancy of at least 3 months and who have had a positive response to a trial dose of intrathecal analgesic. However, the complication rate is relatively high, and information about long-term outcomes is lacking. Moreover, there are little data regarding the effect of intrathecal opioid therapy on other health outcomes, such as degree of disability, ability to work, or overall health status."

ECRI Institute Conclusions

Implantable infusion pumps are reserved for individuals for whom conservative treatments and in some cases, surgery, have failed and surgical correction of cause(s) of pain is not an option. To meet inclusion criteria for enrollment in the case series we identified, patients typically had to have no alternative treatment available. Therefore, implantable infusion pumps are typically considered a treatment of 'last resort.' Because CNCP patients who are candidates for implantable infusion pumps typically have failed multiple other treatments (such as medication delivered by other means, physical therapy, and/or surgery, as described in the background section) and many have had severe pain lasting for years, they seem unlikely to experience a spontaneous remission in pain. The case series identified by our searches that met all inclusion criteria, enrolled patients with a variety of noncancer pain conditions and treated them with different types of infused opioids and adjuvants. Because they all addressed the key question of whether implantable infusion pumps are associated with changes in outcomes, we combined them in meta-analysis wherever possible, with the intent of using statistical techniques to investigate the importance of clinical differences.

Each individual study had a significant mean reduction in pain from baseline. On average, the patients went from having severe pain at baseline to having moderate pain at long-term follow-up. However, the average amount of pain relief from study to study was inconsistent. Due to the resulting instability we rated the evidence "unstable" and did not draw quantitative conclusion regarding the size of pain reduction, although we were able to draw the qualitative conclusion that average pain was reduced with strength of evidence rating of "weak." As 98% of patients who received pumps are included in the long-term pain outcomes data, bias due to attrition should be minimal. We calculated the proportion of patients that had 25% pain relief from baseline (56.3%, 95% CI 37.7%-99.9%) and 50% pain relief from baseline (40.8%, 95% CI 25.2%-58.5%), however, due to quantitative instability we drew no conclusions how many patients attain these levels of pain relief, although we can determine from this calculation that some do and some do not.

That this data come from uncontrolled case series should be considered when interpreting this finding. It is possible that some placebo effect may account for part of the pain relief attained. However, a Cochrane Review that evaluated the influence of placebo interventions for clinical conditions including pain, found a possible placebo effect on reduction of patient-reported pain (although the authors note that it is unclear whether this effect size is clinically importance, and that it cannot be clearly distinguished from other potential sources of bias). The size of this effect was estimated at a SMD of -0.25 (95% CI -0.35 to -0.16), which corresponds to a change in VAS of 6/100 (or 0.6/10).(4,5) The SMD and VAS attributed to a placebo effect are much smaller than the pooled SMD in this report.

Only a subset of studies contributed data to secondary outcomes quality of life, functional status, and employment rate. It is unclear why these data were not collected or reported in the other studies, but it is possible that outcomes may not have been reported based upon findings. Too few studies reported usable data on quality of life or functional status to enable the formation of evidence-based conclusions. Although four studies reported employment rates, due to quantitative differences among the studies we drew no conclusions regarding return to employment. Use of systemic pain medications and adjuvant medications decreased overall after pump implantation in all studies reporting that outcome. The quantity of infused medication increased over time, but the reasons for this are unclear. Findings for all effectiveness and dosing outcomes are summarized in Table 28.

Not all patients had favorable treatment outcomes. Some patients in the included studies (or their physicians) were so dissatisfied with adverse events or insufficient pain relief that they withdrew from the studies. This does not necessarily mean that infusion pump therapy was discontinued altogether; patients may have continued infusion therapy with a different physician or under different protocols. The rate of withdrawal due to insufficient pain relief among patients treated with intrathecal opioids determined in this review (8.0% [95% CI 3.8%-15.8%]) ranged widely, but the point estimate did not dramatically differ

from the withdrawal rate among CNCP patients receiving oral (11.9% [95% CI 7.8%-17.7%]) or transdermal (5.8% [95% CI-4.2%-7.3%]) opioids determined in a recent published systematic review.(97) The rate of withdrawal due to adverse events was lower among patients receiving opioids intrathecally in this review (8.3% [95% CI 4.4%-15.1%]) than among patients receiving oral (32.5% [95% CI 26%.1-39.6%]) opioids and similar to the rate of withdrawal from studies on transdermal (8.0% [95% CI 4.1-15.2]) opioids.(97) These findings should be considered in the context that patients in the population receiving opioids by infusion pump have previously failed conservative (e.g., oral, transdermal opioids) therapy. Further, although quantitative instability precluded firm conclusions regarding the proportion of patients who attain clinically significant pain relief, the summary data suggests that some do not attain this level of pain relief.

We examined case series and MAUDE to profile the safety of implanted infusion pumps. No serious drug-related adverse events or effects were reported by the clinical trials. However, some serious pump-related events, primarily reoperation due to pump technical failure, were reported in the case series. Use of meta-analysis to determine the rates of adverse events is not currently possible due to differences in reporting among studies. In MAUDE, a total of 975 relevant reports were identified among patients using implantable infusion pumps for any indication. This was an identified subset of approximately 9,000 MAUDE reports and we filtered for relevance to this topic to reach 975 relevant reports. Although the majority of the reports were on non-serious events and effects, serious events and effects, including paralysis and death, were reported. Because the number of people who have received an implantable pump in the United States is unclear, determining the rates of these events is not possible. Also, these reports include some events that were not definitively attributed to the pumps. Harms noted in Medtronic safety alerts, FDA letters, and other sources of information include catheter dysfunction, granuloma at catheter time, endocrine dysfunction, and early death after pump implantation.

Fear that an individual with CNCP may develop psychological dependence on drugs during long-term administration is a potential barrier to treatment with opioids. However, the incidence of observed signs of opioid addiction was rarely reported in the body of evidence considered in this review (one case of suspected addiction or abuse reported). Three of the studies in this review screened out patients with a history of opioid or substance addiction or abuse, and eight screened for unspecified psychological contraindications (which may have included addictive/abusive history). These patients were therefore selected with the intent of minimizing the risk of addiction and abuse. Further, adjuvant drug use, including oral opioid use, decreased in all studies that reported ancillary drug use. All studies on the efficacy and safety of opioids should prospectively collect data on abuse and addiction using validated diagnostic criteria. Given the complexity of definitively diagnosing opioid addiction (see, e.g., Ballentyne(98)) and in the interest of capturing the overall effect of opioid therapy on health in general, we sought to analyze health-related quality of life and functional status outcomes in this review. However, insufficient data were available to enable the formation of any evidence-based conclusions.

In general, data describing long-term safety and efficacy of implantable infusion pumps for CNCP are limited in terms of quantity and internal validity, precluding the formation of evidence-based conclusions supported by strong qualitative or stable quantitative evidence. Further, only a minority of studies reported secondary outcomes such as functional status or quality of life and were suitable for inclusion in those outcomes. The fact that only a subset of studies that met general inclusion criteria contributed data to these outcomes increases the possibility of bias due to outcome censoring. An evidence base of low quality provides only weak evidence from which to draw qualitative conclusions and only low-stability evidence from which to draw quantitative conclusions. Some of the quantitative estimates were not robust upon sensitivity analyses, which mean that an estimate of the size of a treatment effect cannot be accurately estimated with the currently available evidence. These quality ratings indicate that the evidence supporting our conclusions may be subject to change, and that there is potential that findings of future studies may overturn these conclusions. Unfortunately, we found no studies that attempted to identify differential safety and/or efficacy in among patient populations, or prognostic factors for drop-out, and a

paucity of evidence precluded us from thoroughly investigating such factors in this assessment. Studies designed to examine patient- and treatment-related factors predicting long-term success with opioid therapy would be extremely useful for optimal patient selection. Potentially meaningful prognostic factors could include severity and cause of pain, co-morbidities, general health, and motivation to improve.

In general, we deemed the evidence insufficient to determine whether long-term costs of implantable infusion pump treatment are different from those of non-pump treatment. Our reasons for this determination are described next.

The de Lissovoy analysis(9) was conducted at least 11 years ago using simulated patients within a deterministic Markov model, and more advanced methods are now available for more accurate cost analysis. Authors did incorporate many important costs, including pump replacement and adverse events, and the estimated five-year total costs for the two treatments were very similar ($82,893 for the pump vs. $85,186 for non-pump). However, sensitivity analyses revealed very wide ranges for pump treatment (from $53,468 to $125,102). This wide range of uncertainty casts doubt on any conclusion about comparative long-term costs.

The Kumar analysis(10) was conducted in Canada eight years ago. Canadian costs structures are quite different from those in the US. Also, interpretation of the study results was complicated by the differential selection of patients in one group but not the other, which may have biased the study to find lower costs in the pump group. These two issues meant that we did not draw conclusions based on its results.

The other two analyses were also judged inconclusive for long-term comparative costs for chronic non-cancer pain. The Anderson trial(11) focused on the costs of different screening methods for the pump, rather than costs of pump vs. non-pump treatment. The Reden and Anders analysis may have included patients without chronic non-cancer pain, so its precise relevance is unknown. Also, authors attempted to estimate the cost of non-pump treatment using costs incurred in the single month prior to pump implantation. This latter cost (about $4,000 per month) was much higher than the costs reported in the other analyses (about $1,000 per month), calling into question any comparison with pump treatment costs.

Summary

The only kind of evidence about whether implantable infusion pumps are effective for patients with chronic noncancer pain comes from uncontrolled case series,. On average, patients in case series reported considerably less pain after the implantation of an infusion pump. It was not possible to determine precisely how much pain relief the average patient had due to inconsistency in average pain relief among studies. While some individuals attained meaningful levels of pain relief, some did not. It was not possible to determine precisely what percentage of patients did or did not attain meaningful pain relief due to inconsistent findings among studies. Although four studies reported an increase in the proportion of patients who could work after pump implantation, this finding was not statistically significant for all studies or when the studies were pooled. Quality of life and functional status were too sparsely reported to permit and conclusions. Dose of infused drug tended to increase over time, while use of other medications decreased; however, the reasons for these changes were unclear. Many minor adverse events and some device-related events requiring surgical intervention occurred in the case series. Serious drug- and device-related adverse events, including death, were identified in the MAUDE database and in FDA recalls and Medtronic safety alerts; however, the actual rate of these events is unknown.

No included studies attempted to identify patient factors related to safety, efficacy, or drop-out. No factors were identified in our own statistical analysis, but this may be due to the limited number of studies available and sparse reporting. Studies designed to examine patient- and treatment-related factors predicting long-term success with opioid therapy would be extremely useful for optimum patient selection. Potentially meaningful prognostic factors could include baseline severity and cause of pain, comorbidities, general health, and motivation to improve.

Two five-year cost analyses compared implanted infusion pumps with continued conservative therapy, and both suggested that the greater upfront cost of an implantable pump is eventually offset by the lower long-term costs of pain management (at about 2-3 years).

Table 28. Summary of Effectiveness and Safety Findings

Outcome		k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Pain	Continuous	7	143	Low	89.2%	SMD	2.34 (1.46-3.24)	Yes	Weak	No	Unstable	Drug infusion with an implantable pump leads to clinically significant pain relief in patients with CNCP. (Strength of evidence: Weak). No quantitative conclusion drawn due to differences among studies.
	≥25% Pain Relief	6	123	Low	66.5%	Proportion	56.3% (33.7%-73.3%)	NA	Weak	No	Unstable	No quantitative conclusion drawn due to differences among studies.
	≥50% Pain Relief	7	150	Low	67.6%	Proportion	40.8% (25.2%-58.5%)	NA	Weak	No	Unstable	No quantitative conclusion drawn due to differences among studies.
Discontinuation from Clinical Study due to insufficient pain relief		5	102	Low	<0.01%	Proportion	8.0% (3.8%-15.8%)	Yes	Weak	No	Low	Of patients who began treatment with an implantable pump used for intrathecal opioid delivery for CNCP, 8.0% (95% CI 3.8%-15.8%) discontinued treatment in the clinical trial due to insufficient pain relief. (Stability of evidence: Low)

Outcome	k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Quality of Life	2	48	Low	-	-	-	No	Inconclusive	-	Unstable	It is not possible to determine whether long-term use of intrathecal opioids change the quality of life for patients with CNCP, because the two studies that met inclusion criteria for this outcome had inconsistent findings (one found improvement, but the other did not)
Functional Status	1	24		-	-	-	No	Inconclusive	-	Unstable	Because only one study reported this outcome, there was an insufficient quantity of evidence to permit a conclusion for this outcome.
Employment Status	4	83	Low	36.7%	Odds Ratio	-	No	Inconclusive	No	Unstable	The current evidence is insufficient to determine whether implantable infusion pumps are associated with a change in employment status among patients with chronic non-cancer pain.
Use of other medications and other treatments	9	347	-	-	-	-	Yes	-	-	-	Intrathecal administration of opioids by implantable pump was associated with an overall decrease in the quantity of other drugs taken or a decrease in the proportion of patients taking other drugs.

Outcome	k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Changes in quantity of infused medication administered	10	218	-	-	-	-	Yes	-	-	-	The dose of medication infused by an implantable infusion pump increased over time, but the amount of dose change is not predictable from available studies.
Discontinuation from Clinical Study due to adverse events	7	132	Low	<0.01%	Proportion	8.3% (4.4%-15.1%)	Yes	NA	Yes	Low	Of patients with CNCP who begin intrathecal opioid therapy with an implanted pump, 8.3% (95% CI 4.4% to 15.1%) patients discontinued participation in the clinical study due to adverse events and effects. (Stability of estimate: Low).
Adverse Events (Clinical Studies)	13	231		-	-	-	-	-	-	-	No serious drug-related adverse events or effects were reported by the clinical trials. However, serious pump-related events, primarily reoperation due to pump technical failure, were reported. Use of meta-analysis to determine the rates of adverse events is not possible due to differences in reporting among studies.

Outcome	k =	n =	Internal Validity Score of Evidence Base	I^2	Meta-Analysis Unit	Random-Effects Meta-Analyses (95% CI)	Qualitatively Robust?	Strength of Evidence	Quantitatively Robust?	Stability of Evidence	Conclusion
Adverse Events (MAUDE)	NA	NR		-	-	-	-	-	-	-	A total of 975 relevant reports were identified in the Manufacturer and User Facility Device Experience Database (MAUDE). Although the majority of the reports were on non-serious events and effects, many serious events and effects, including paralysis and death, were reported.

CI Confidence interval.
k Number of studies.
n Number of patients for whom outcome analyzed.
NA Not applicable.
NR Not reported.
SMD Standardized mean difference.

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174. Kanoff R. (Professor and Chairman, Division of Neurosurgery. Philadelphia College of Osteopathic Medicine). Personal communication. 2008 Jul 8. 1 p.

Appendix A. Literature Search Methods

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Electronic Searches

We searched the following databases for relevant information:

Name	Date limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1990 through June 2, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1990 through June 2, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
Healthcare Standards	April 8, 2008	ECRI Institute
International Health Technology Assessment (IHTA)	Through June 2, 2008	ECRI Institute
MEDLINE	1990 through June 2, 2008	OVID
PreMEDLINE	Searched June 2, 2008	OVID
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	April 8, 2008	http://www.ngc.gov

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

MAUDE

The MAUDE database of adverse events reports was searched through ECRI Institute's Health Devices System interface, Searches were conducted using the FDA procode LKK (pump, infusion, implanted, programmable) and further refined with keywords: intraspinal, intrathecal, subararchoid, subdural, extradural, epidural, Synchromed, Insfusaid, Therex, Isomed, Secor, Gemstar. This refinement eliminated adverse events reports from implantable infusion pumps for purposes other than treating patients for chronic pain (e.g. insulin pumps).

Grey Literature

ECRI Institute's extensive experience in identifying grey literature stems from decades of developing content for and maintaining applications such as the Healthcare Standards Database and Directory and the International Health Technology Assessment (IHTA) database. Under contract to the National Library of Medicine (NLM), ECRI Institute staff also selects and indexes health services research-related content for the NLM Catalog (LOCATORPLUS) and Medline. Searches are conducted using multiple Internet search engines (e.g. Google, Kartoo), to identify relevant societies, associations, manufacturers, government agencies, etc. These sites are then extensively mined for materials relevant to the topic of the review. Additional known portals and collections of grey literature are also reviewed for each topic.

Commercial Payer Policies

ECRI Institute's list of commercial payers is composed of payers who post their coverage policies freely on the internet. Although ECRI Institute limits its targeted coverage searches to freely available Web sites and those through America's Health Information Plans (AHIP) Web site, additional policies are sometimes identified through our searches of the grey literature.

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Device-related complications	Exp catheter complication/ Exp catheter-related complications/ Obstruction Catheter occlusion *(this term is also included under catheter complication in EMBASE and equipment failure in CINAHL)* Exp equipment failure/ Power sources Electric battery Cicatrix Exp cicatrix/ Exp scar/	Battery Catheter$ Detach$ Disconnect$ Dislocation Failure$ Infection$ Kink$ Malfunction$ Migration Obstruction Pocket Scar$
Implantable		Continuous Implant$ Subcutaneous$
Intrathecal/intraspinal	Injections, intraspinal Injections, spinal Infusions, intraspinal Intrathecal drug administration Subarachnoid space	Continuous infusion Intraspinal Intrathecal Subarachnoid

Concept	Controlled Vocabulary	Keywords
Opioids	Exp analgesics, opioid/ Exp narcotics/ Exp narcotic analgesic agent/ Exp opiates/	Actiq Avinza Combunox Depodur Dolophine Duragesic Duramorph Fentanyl Fentora Infumorph Ionsys Kadian Methadone Methadose Morphine MS contin Nasalfent Numorphan Opana Oxycodone Oxycontin Oxymorphone Percocet Percodan Sufenta Sufentanil Tramadol Ultram
Other specific drugs		Baclofen Ziconotide

Concept	Controlled Vocabulary	Keywords
Pain	Exp pain/ Pain, intractable	Chronic pain Intractable pain Persistent pain Refractory pain
Painful conditions	Exp arthropathy/ Exp back pain/ Exp backache/ Exp joint diseases/ Exp multiple sclerosis/ Exp musculoskeletal disease/ Exp musculoskeletal diseases/	Allodynia Arterosclerosis obliterans Arthrit$ Back Chronic pancreatitis Fibrositis Fibromyalgia MS Neck Neuralgia Neuropath$ Phantom Sciatica
Pumps	Drug delivery systems Exp drug delivery system/ Infusion pump Infusion pumps, implantable Catheters, indwelling Indwelling catheter	Implant$ adj2 pump$ Isomed Programmable Synchromed Therex

Concept	Controlled Vocabulary	Keywords
Excluded concepts	Exp neoplasm/ Exp neoplasms/	Cancer Carcinoma Childbirth Labor Labour Postop Post operative Post-op Post-operative

CINAHL/EMBASE/MEDLINE

English language, human

1990 - 2008

Set Number	Concept	Search statement	Number Identified
1	Implantable infusion pumps	Exp drug delivery system/ or (Drug delivery systems or Infusion pump or Infusion pumps, implantable or catheters indwelling or indwelling catheter).de.	179950
2		((Intrathecal drug administration or injections spinal or injection, intraspinal).de. or Intrathecal or intraspinal or epidural or subarachnoid or implant$) and (pump$ or port$ or continuous)	40759
3	Combine sets	1 or 2 English & human & 1990 – 2008	215142 86444
4	Pain	(exp pain/ or pain$.ti,ab.) and (chronic or intractable or refractory or persistent).ti,ab.	130678
5		Pain intractable.de.	4670
6		(soft tissue or (pancreatitis and chronic) or arteriosclerosis obliterans or fibromyalgia or fibrositis or arthrit$ or back or neck or tmj or MS or phantom or allodynia or sciatica or neuralgia or neuropath$).ti,ab. or neck pain.de.	1025681
7		exp musculoskeletal diseases/ or exp musculoskeletal disease/ or exp joint diseases/ or exp arthropathy/ or exp back pain/ or exp backache/ or exp multiple sclerosis/	1464638
8	Opioids	Exp analgesics, opioid/ or Exp narcotics/ or Exp narcotic analgesic agent/ or Exp opiates/	254199
9		Actiq or Avinza or Combunox or Depodur or Dolophine or Duragesic or Duramorph or Fentanyl or Fentora or Infumorph or Ionsys or Kadian or Methadone or Methadose or Morphine or MS contin or Nasalfent or Numorphan or Opana or Oxycodone or Oxycontin or Oxymorphone or Percocet or Percodan or Sufenta or Sufentanil or Tramadol or Ultram	162122
10	Other specific drugs	Ziconotide or baclofen	15223
11	Combine sets	or/4-10	2501120
12	Combine sets	3 and 11	13231
13	Limit by publication type	12 not ((letter or editorial or news or comment or note or conference paper).de. or (letter or editorial or news or comment).pt.)	11920
14	Limit by concept	13 not (Exp neoplasm/ or Exp neoplasms/ or Cancer or Carcinoma or Childbirth or intrapartum or Labor or Labour or perinatal or postpartum or Postop or Post operative or Post-op or Post-operative)	8601
15*	Eliminate overlap	Remove duplicates from 14	6994
16	Adverse events	3 and ((ae or co or side effect or contraindication).fs. or (harm$ or iatrogen$ or nosocom$ or hazard$ or nnh).ti,ab.) and pump$	3216
17		3 and (Exp catheter complication/ or Exp catheter-related complications/ or Exp equipment failure/ or Exp cicatrix/ or Exp scar/ or (Obstruction or Catheter occlusion or Power sources or Electric battery or Cicatrix).de.)	1921

Set Number	Concept	Search statement	Number Identified
18		3 and (Batter$ or (Catheter$ and (Detach$ or Disconnect$ or Dislocat$ or Failure$ or infect$ or Kink$ or Malfunction$ or Migrat$ or Obstruct$)) or Pocket$ or Scar$)	7755
19	Combine sets	or/16-18	10860
20	Eliminate overlap	Remove duplicates from 19	9236
21*	Limit by publication type	20 not ((letter or editorial or news or comment or note or conference paper).de. or (letter or editorial or news or comment).pt.)	8375
22	Cost-effectiveness	3 and (ec.fs. or exp cost and cost analysis/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.)	3168
23		22 not ((letter or editorial or news or comment or note or conference paper).de. or (letter or editorial or news or comment).pt.)	2944
24*	Eliminate overlap	Remove duplicates from 23	2522

* Findings from set numbers 15, 21, and 24 were screened for inclusion

Table 29. Excluded Studies

Study	Reason for Exclusion
Effectiveness/Safety: Key Questions 1,2 and 3	
Abs et al. 2000(85)	Retrospective and patient selection method not reported as consecutive or random
Ackerman et al. 2003(99)	Retrospective and patient selection method not reported as consecutive or random
Albright and Ferson 2006(100)	Pain not an inclusion criterion
Albright et al. 2003(101)	Pain not an inclusion criterion
Albright et al. 2004(102)	Pain not an inclusion criterion
Auld et al. 1985(103)	Retrospective and patient selection method not reported as consecutive or random
Awaad et al. 2008(104)	Pain not an inclusion criterion
Bedder et al. 1996(105)	Not a clinical study (literature review/tutorial); focused on epidural administration
Ben smail et al. 2006(106)	Pain not an inclusion criterion
Bjornson et al. 2003(107)	Pain not an inclusion criterion
Boviatsis et al.(108)	Pain not an inclusion criterion
Brown et al. 1999(109)	Retrospective and patient selection method not reported as consecutive or random
Dachy and Dan 2004(110)	Pain not an inclusion criterion
Dahm et al. 1998(111)	Not a clinical study (literature review/tutorial)
Deer et al. 2004(70)	Pain and quality of life outcomes excluded because measures of variance not reported – this study was included for other outcomes
Doleys et al. 1998(112)	Not a clinical study (Telephone interview, patient selection methods not reported)
Ellis et al. 2008(113)	Substantial portion of patients (~33%) have cancer pain, outcomes not reported separately
Ethans et al. 2005(114)	Pain not an inclusion criterion
Fitzgerald et al. 2004(115)	Pain not an inclusion criterion
Francisco and Boake 2003(116)	Pain not an inclusion criterion
Francisco et al. 2005(117)	Pain not an inclusion criterion
Gay et al. 2002(118)	Substantial portion of patients (35%) have cancer pain, outcomes not reported separately; Retrospective and patients not randomly or consecutively selected
Guillaume et al. 2005(119)	Mean baseline pain level <5/10 VAS
Hassenbusch et al. 1991(43)	N <10
Hassenbusch et al. 1995(120)	Retrospective and patient selection method not reported as consecutive or random
Hildebrand et al. 2001(121)	Retrospective and patient selection method not reported as consecutive or random
Ivanhoe et al. 2006(122)	Pain not an inclusion criterion
Kikuchi et al. 1999(123)	Duration of treatment less than 6 months

Study	Reason for Exclusion
Koulousakis and Kuchta 2007(124)	Pain not an inclusion criterion
Kouousakis et al. 2007(125)	Substantial portion of patients (30%) have cancer pain, outcomes not reported separately
Krach et al. 2004(126)	Pain not an inclusion criterion
Krach et al. 2005(127)	Pain not an inclusion criterion
Krach et al. 2007(128)	Pain not an inclusion criterion
Likar et al. 1999(129)	Retrospective and patient selection method not reported as consecutive or random
Lind et al. 2004(130)	Mean baseline pain level <5/10 VAS
Lind et al. 2008(131)	N <10
Loubser et al. 1996(132)	N <10 per group
Maniker et al. 1991(133)	Cancer pain
Middel et al. 1997(134)	Pain not an inclusion criterion
Mironer et al. 2002(135)	Duration of treatment less than 6 months
Molloy et al. 2006(136)	N <10 received an implantable infusion pump
Motta et al. 2008(137)	Pain not an inclusion criterion
Nielsen and Sinkjaer 2004(138)	Pain not an inclusion criterion
Njee et al. 2004(139)	Not a clinical study: Survey with low response rate and reporting on only a subset of possible patients
Ordia et al.(140)	Pain not an inclusion criterion
Paice et al. 1996(141)	Not a clinical study (Survey with very low response rate (52%))
Penn et al.(142)	Substantial portion of patients (81%) have cancer pain, outcomes not reported separately
Raffaeli et al. 2008(143)	Retrospective and patients not reported as consecutive or random
Raphael et al. 2002(144)	Not a clinical study
Rawlins 2004(145)	Pain not an inclusion criterion
Remy-Neris et al. 2003(146)	Pain not an inclusion criterion
Saltari et al. 2007(147)	Another version of Shaladi et al. 2007(71)
Smith et al. 2002(148)	Duration of treatment less than 6 months
Staats et al. 2007(149)	Does not address a key question; no outcomes of interest
Stokic et al. 2005(150)	Pain not an inclusion criterion
Valentino et al. 1993(151)	Retrospective and patient selection method not reported as consecutive or random
Vender et al. 2006(152)	Pain not an inclusion criterion
Wallace et al. 2008(153)	Duration of treatment less than 6 months

Study	Reason for Exclusion
Willis et al. 1999(154)	Not a clinical study (Telephone interview)
Winkelmuller and Winkelmuller 1996(155)	Retrospective and patient selection method not reported as consecutive or random
Yasser et al. 20003(104)	Pain not an inclusion criterion
Yoshida et al. 1986(156)	N <10
Zuniga et al. 2000(157)	N <10
Cost Issues: Key Question 4	
Aldrete (1997)(158)	Only three weeks treatment duration
Bedder (1991)(159)	Only 8/20 patients (40%) had non-malignant pain, and also the study examined pumps that are no longer available.
Hassenbusch (1997)(160)	A review, not a cost analysis. One model was developed for cancer patients, and the other model was detailed in a different article (the included article by de Lissovoy).
Lachaine (2007)(161)	Did not mention the costs of implantable infusion pump use.
Mueller-Schwefe (1999)(162)	A review, not a cost analysis
Nguyen (2004)(163)	A review, not a cost analysis
Rodriguez (2007)(164)	Did not mention the costs of implantable infusion pump use.
Smith (2007)(165)	Did not mention the costs of implantable infusion pump use.
Staats (2007)(149)	Did not mention the costs of implantable infusion pump use.

Appendix B. Internal Validity of Literature and Evidence Rating

Internal Validity Scale

In order to grade the quality of studies, we use an internal validity rating scale. This scale was developed by ECRI Institute to assess the internal validity of studies using domains identified as important factors by experts in the field.(166-168) This scale allows us to calculate an internal validity score based on *a priori* criteria. The questions in the scale are worded so that study design aspects that provide evidence with good internal validity result in "Yes" answers, design aspects that create potential for bias result in "No", and design aspects that are inadequately described result in an answer of "NR" (not reported).

Table 30. ECRI Institute Before/After Study Internal Validity Scale

Item Number	Quality Item
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?
4	Was the study prospectively planned?
5	Did ≤5% of patients receive ancillary treatment(s)?
6	Was compliance with treatment ≥85%?
7	Was the outcome measure of interest objective and was it objectively measured?
8	Was a standard instrument used to measure the outcome?
9	Did ≥85% of the patients contribute data to this outcome?
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?

To compute these summary scores, we made the following calculations. We first converted the individual item answers to numeric scores by counting 1 for each Yes answer, -1 for each No, and -0.5 for each NR. The raw score is normalized by adding 10 and dividing by 5.

Strength- and Stability-of-Evidence System

After grading the body of evidence for a particular question on each of the five domains (internal validity, quantity, consistency, robustness, and magnitude of effect), we applied the grades to a system that divided the strength of the evidence supporting each qualitative conclusion into one of four ratings: strong, moderate, weak, or inconclusive.(64) In addition, the system categorized the stability of each quantitative estimated into one of four ratings: high, moderate, low, or unstable. The meanings of these ratings are summarized in the table below.

Table 31. Categories of Strength of Evidence Supporting Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion (Direction of Effect)	
Strong Evidence	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate Evidence	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature at this time.
Weak Evidence	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Inconclusive Evidence	Although some evidence exists, this evidence is not of sufficient strength to warrant drawing an evidence-based conclusion from it. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Quantitative Conclusion (Magnitude of Effect)	
High Stability	The estimate of treatment effect included in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate Stability	The estimate of treatment effect included in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature at this time.
Low Stability	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature at this time.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

To arrive at these strength and stability ratings, we applied the ECRI Institute Strength and Stability of Evidence System. The methods we used to resolve these decision points appear next.

Decision Point 1: Determining Internal Validity of Individual Studies

Decision Point 1 has two purposes: 1) to assess the internal validity of each included study; 2) to provide a means of excluding studies that are so prone to bias that their results cannot be considered useful.
To assess the internal validity of each of the studies included in this assessment, we applied the ECRI Institute Before/After Study Internal validity Scale (see Table 30, above). Each study is assigned a score from 0 to 10, where a score of 10 indicates an ideal study, and a score of 0 indicates a study of the poorest possible internal validity. For internal validity assessments outcome-by-outcome, refer to the appendix for that key question.

One item used to determine the internal validity of individual studies in this report is source of funding. Sources of funding reported in the included studies are listed below in

Table 32. Funding Sources

Study	Year	Reported Source of Funding (as stated in publication)

Krames and Lanning(65)	1993	None reported
Kanoff(7)	1994	Medtronic Corporation provided technical assistance for infusion pump use, and provided a grant for preparation of the manuscript
Hassenbusch et al.(39)	1995	None reported
Tutak and Doleys(66)	1996	Supported in part by Wyeth-Ayerst Laboratories and Medtronic
de Lissovoy et al.(9)*	1997	Funded through a contract between Medtronic Inc. (Minneapolis, MN) and the Battelle Memorial Institute (Washington, DC)
Angel et al.(67)	1998	None reported
Anderson and Burchiel(6)	1999	Supported in part by funding from Medtronic Inc.
Kumar et al.(68)	2001	None reported
Mironer and Tollison(55)	2001	None reported
Rainov et al.(69)	2001	This study was supported in part by a research grant from Medtronic GmbH, Dusseldorf, Germany
Kumar et al.(10)*	2002	Funding source not reported, but authors stated that they have "no financial interest in the subject under discussion."
Anderson et al.(11)	2003	This work was funded by a grant from Medtronic Inc
Deer et al.(70)	2004	None reported
Thimineur et al.(8)	2004	Supported by grant from Medtronic Inc.
Reden and Anders(12)*	2006	Medtronic, Inc. (Minneapolis, MN)
Shaladi et al.(71)	2007	None reported

* These cost and cost-effectiveness studies were not rated for internal validity because the strength and stability of evidence in that key question was not rated

Decision Point 2: Determine Internal Validity of Evidence Base

We classified the overall internal validity of the evidence base by taking the median internal validity score of the individual studies. We used the median because it is the appropriate measure of central tendency to represent the "typical" internal validity score, and is less sensitive to outliers than the mean. Depending on the overall internal validity scores for each outcome, we then followed the high, moderate, or low internal validity branch of the system.

The quality of the evidence base sets an upper limit on judgments of the strength and stability of the evidence. For example, the strength of evidence can be weak, moderate, or strong if the evidence base is of high internal validity, but the strength can never be strong if the evidence base is of moderate or low internal validity.

To determine whether the evidence base was of Moderate, or Low internal validity, we used the thresholds listed in Table 33. The definitions for what constitutes moderate, low, or unacceptably low internal validity evidence were determined *a priori* by a committee of four methodologists. Because case series have no control group, they are typically not considered to provide high-quality evidence. Therefore, the maximum possible internal validity category is moderate. Since the internal validity was

determined separately for each outcome, a study that scored as high internal validity for one outcome might score as moderate internal validity for another outcome.

Table 33. Internal Validity of Evidence Base

Internal Validity Category	Range of Scores
Moderate	7.5 to 8.4
Low	5.0 to 7.5
Unacceptable	<5.0

Decision Point 3: Is Quantitative Analysis Possible?

The answer to Decision Point 3 depends upon the adequacy of reporting in available studies as well as the number of available studies. In order to conduct a quantitative analysis of a given outcome, the data for that outcome must be reported in at least three studies in a manner that allows the data to be pooled in a meta-analysis. If fewer than three studies are available, no quantitative analysis is usually possible regardless of reporting. For continuous outcomes, meta-analysis is possible when the pertinent studies either report effect sizes and standard errors, or there is sufficient reported information for both effect sizes and standard errors to be calculated. For dichotomous outcomes, meta-analysis is possible when the pertinent studies report the total number of patients in each group as well as the number of events in each group.

We typically do not pool data when fewer than 75% of studies that met general inclusion criteria report a given outcome and permit determination of the effect size and its dispersion, either by direct reporting from the trial or calculations based on reported information. This is because of the possibility that other studies did not report the outcome to censor it, increasing the risk of bias in the available data. However, for this report we proceeded with analysis to show what the available data does say, to support decision making. We caution that the generalizability of these data sets is unknown.

In addition, we typically only conduct meta-analysis when the findings are potentially informative. When there are only a small number of patients in an evidence base, statistical tests generally do not perform well. Under such circumstances, statistics cannot determine whether a true difference exists between treatments. This means that no clear conclusion can be drawn. For this decision point, we determined whether the precision of an evidence base was sufficient to permit a conclusion. Statistically significant results are potentially conclusive because they mean that a treatment effect may exist. Statistically non-significant results are also potentially conclusive, but only if they exclude the possibility that a clinically significant treatment effect exists.

If no quantitative analysis is possible, then we moved directly to Decision Point 8 to begin a qualitative analysis.

When considering the summary effect size from a meta-analysis (or the effect size from a single study), the effect can be deemed "informative" in one of three ways:

1. The summary effect size is statistically significantly different from 0. This would be indicated whenever the confidence interval does not overlap 0.
2. The summary effect size is not statistically significantly different from 0, but the confidence intervals are narrow enough to exclude the possibility that a *clinically significant difference* exists.
3. The summary effect size is not statistically significantly different from 0, but the confidence intervals are narrow enough to exclude the possibility that a *substantial difference* exists. This

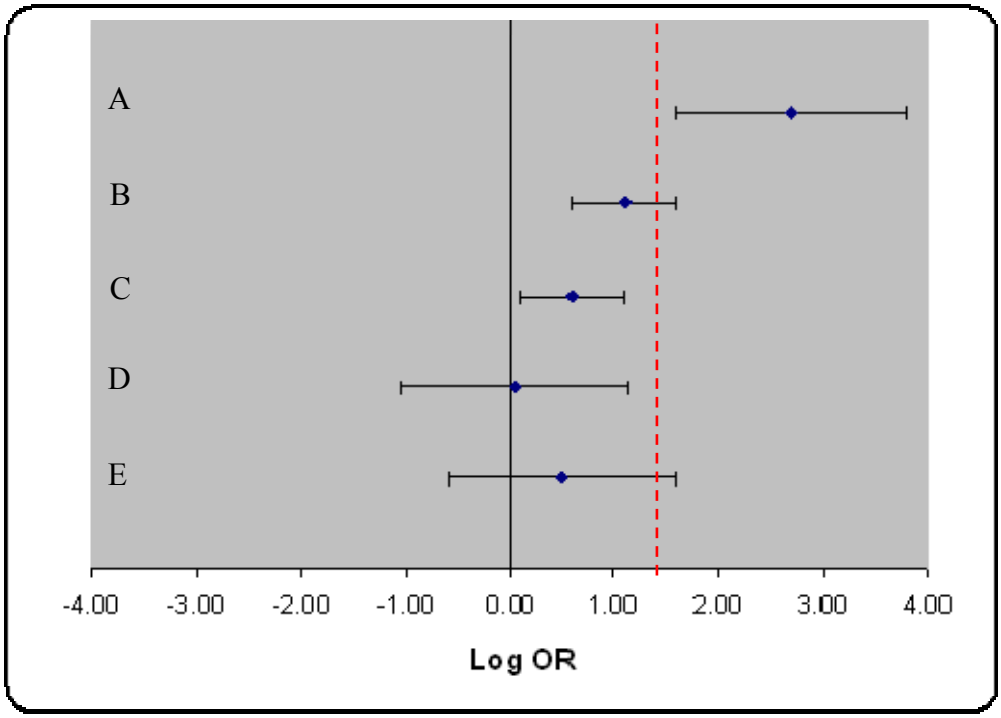
possibility is included to address situations when even a very small effect can be considered "clinically significant" (e.g., a difference in mortality rates), but the effect may not be "substantial".

Decision Point 4: Are Data Quantitatively Consistent (Not substantially heterogenous)?

This decision point was used only if the answer to Decision Point 3 was Yes. Consistency refers to the extent to which the results of studies in an evidence base agree with each other.(169) The more consistent the evidence, the more precise a summary estimate of treatment effect derived from the evidence base. Quantitative consistency refers to consistency tested in a meta-analysis using Higgins and Thompson's I^2 statistic.(75) We considered the evidence base to be quantitatively consistent when I^2 <50%.

If the evidence base was quantitatively consistent, we combined the results in a meta-analysis and report the point estimate and 95% confidence intervals. We tested the stability of the quantitative summary estimate in Decision Point 5. If it was not homogeneous, we combined the results in meta-analysis and stress the instability of the point estimate, preferring to rely upon the more conservative range of 95% confidence limits. Having obtained a summary effect size estimate, we will then determine whether this estimate is informative. That is, we will determine whether the findings of the meta-analysis allow one to draw a conclusion. To see what is meant by this, consider Figure 15. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure 15. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect and it is also unclear whether the treatment effect is clinically important. This latter finding is thus non-informative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

Robustness was addressed by determining the stability of the summary estimate. A stable summary estimate indicates that the accumulated body of evidence is large enough to have accurately measured the "true" effect size. The stability of summary estimates was tested with cumulative meta-analysis.(78,79) Studies were sequentially added in order of decreasing size into a meta-analysis, and summary estimates calculated for each step. If the summary effect size in any of the last three of these analyses was 5% points higher or 5% points lower than the overall summary effect size, we deemed the estimate to be not robust. We also conducted an impact analysis, in which we removed and replaced each study one at a time to see whether the removal of any single study changed the summary effect size by more than 5% points. If changes to the summary effect size were not greater than 5% points, we deemed it to be robust.

A pre-requisite of an analysis of quantitative robustness is that the 95% confidence interval around a meta-analytic effect size should not exceed a certain range. If the standard deviation of the summary effect is less than or equal to 0.10 (10% difference), then proceed to perform an analysis of quantitative robustness. This number (0.1) is based on the use of 0.1 as the minimum clinically important effect size in terms of the standardized mean difference (SMD). Thus, if the total confidence interval width is less than 0.2, then the point estimate must be within 1 unit of clinical significance, which would pass this initial pre-requisite. We refer to the point estimate of the meta-analytic summary statistic as SESfull.

Robustness was tested by performing a one-study removed meta-analysis, and a cumulative meta-analysis.

To perform cumulative meta-analysis to evaluate quantitative robustness:

1. Compute effect size with 95% CI for the oldest study
2. Add rest of studies one at a time in order of next-most-recent publication date (by year and then alphabetically)
3. Examine the last two additions (the additions of the two most recent publications). If neither SES of those last two additions differs by more than the minimum clinically significant effect (0.20) size from the preceding SES, and the confidence intervals are not wider than 20% points of the SES, then the evidence base can be considered robust.

To perform an impact analysis to evaluate quantitative robustness:

1. Compute the for the entire evidence base (SES_{full}).
2. Recompute the SES, but without one of the studies. Repeat until the SES has been computed as many times as necessary so that you have computed it without one of the studies each time.
3. If the findings of any of these SES minus one of the studies is different from the SES_{full} by more than 10% points, then the finding is not quantitatively robust.

Decision Points 6 and 7 are relevant only when the evidence base is heterogeneous (see Decision Point 4).

Decision Point 6: Does Meta-Regression Explain Heterogeneity?

Decision Points 6 and 7 are relevant only when the evidence base is substantially heterogeneous (see Decision Point 4).

If we observed heterogeneity, we next attempted (if there were at least 10 studies) to explain the heterogeneity using meta-regression. If there were fewer than 10 studies in this situation, we did not arrive at a quantitative estimate. *A priori*, we planned to use the following factors as predictor variables in meta-regression:

- Duration of treatment

- Opioid(s) administered
- Adjuvant treatments
- Mode of administration
- Characteristics of patient population. To avoid and ecologic fallacy, we will not use average patient characteristics (e.g., mean age of patients in studies), however, comparison of subgroups (e.g., patients over aged 65 and patients younger than age 65) and entire studies (e.g., study only enrolled patients aged 65 and older) may be possible.

For meta-regressions, we planned to perform random-effects meta-regressions in Stata using the permutation test *P*-value, as described by Higgins and Thompson.(77) We decided that a meta-regression could be considered to have explained the heterogeneity if the covariate was statistically significant by the permutation test, and if the *P*-value for the remaining heterogeneity was greater than 0.1. Other rules include the following:

- The number of covariates that will be evaluated given the size of the evidence base.
- What these covariates will be along with the rationale for choosing them.
- Whether "explaining heterogeneity" will require a significant covariate in addition to statistically non-significant heterogeneity, or that only the latter condition will be required
- The criteria that determine whether another predictor variable should be added to the model.
- The criteria that determine which of several models is the "best" model.

Decision Point 7: Is Meta-Regression Model Stable?

Decision Points 6 and 7 are relevant only when the evidence base is heterogeneous (see Decision Point 4).

The purpose of Decision Point 7 is to test the stability of any quantitative findings that may emanate from meta-regression analysis. We used the same robustness test as in Decision Point #5.

Decision Point 8: Are Qualitative Findings Robust?

In this report, we only attempted to draw a qualitative conclusion for outcomes with comparators (e.g., pre-post scores). We did not attempt to draw conclusions for dichotomous conclusions with no comparators (e.g., proportion of patients with at least 50% pain relief, proportion of patients who withdrew from the study for a given reason). For that type of study, quantitative conclusions only were attempted.

For the robustness test, we performed the same cumulative meta-analysis test and impact meta-analysis that we performed for Decision Point #5, except that for this decision point, we considered whether any of the last three analyses had confidence intervals that overlapped 0. If so, we deemed the result to be not qualitatively robust, and if not, we deemed it to be qualitatively robust. For all data we performed a DerSimonian and Laird random-effects meta-analysis.(170)

Decision Point 9: Are Data Qualitatively Consistent?

This Decision Point is used only when the evidence base for an outcome consists of two studies. For our purposes, the two studies were considered qualitatively consistent if they met either of the following two situations: 1) both studies showed a statistically significant effect in the same direction; or 2) neither study showed a statistically significant effect.

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. If a single study finds a large effect with a narrow confidence interval, then new evidence is unlikely to overturn the qualitative conclusion. To resolve this decision point, we examined the 95% confidence interval around the effect size for the study (with two studies, we examined the interval around the random effects summary statistic). If this interval was fully above +0.5 (or if it was fully below -0.5), and the point estimate itself was 0.8 or greater, we considered the effect to be large. Otherwise, we considered it to be not large. For example, an estimate of 0.85 with an interval from +0.6 to +1.1 would be considered a large effect, whereas an estimate of 0.85 with an interval from +0.4 to +1.3 would not be considered a large effect. Another effect that would be considered large is an estimate of -0.85 with an interval from -1.1 to -0.6 (large in the negative direction). The use of 0.5 and 0.8 is based on Cohen,(171) who stated that an effect size of 0.5 was "moderate" and an effect size of 0.8 was "large". Thus, the decision rule required that the point estimate be large and also that it be statistically significantly larger than "moderate". The use of 0.5 and 0.8 applies only to Hedges' d as the measure of effect size.

To determine whether an effect for a dichotomous outcome was "large", we examined the summary odds ratio and its confidence interval. Specifically, if the summary odds ratio was larger than 5 (or below 0.2) and its confidence interval was fully above 2 (or below 0.5), we defined the effect as large. If either or both of these conditions were not met, we defined the effect as not large. The thresholds of 5 and 2 are based on the definitions of "very strong" and "strong" relative risks by the GRADE working group.(172) We used odds ratios rather than relative risks due to the superior mathematical properties of odds ratios.

For conclusions of equivalence, we resolved this decision point by determining whether the magnitude of effect was tiny. For continuous outcomes, we defined tiny as a 95% confidence that was fully within 0.2 of 0. The choice of 0.2 is also based on Cohen,(171) who stated that an effect size of 0.2 was "small"; thus for equivalence we required that the effect be statistically significantly smaller than "small". For dichotomous outcomes, we defined tiny as a 95% confidence interval around the odds ratio that was fully within 1.25 of 0.

We defined a mega-trial as any trial that reported data on 1,000 or more patients.

Below, this system is illustrated in a series of four figures.

Figure 16. General Section

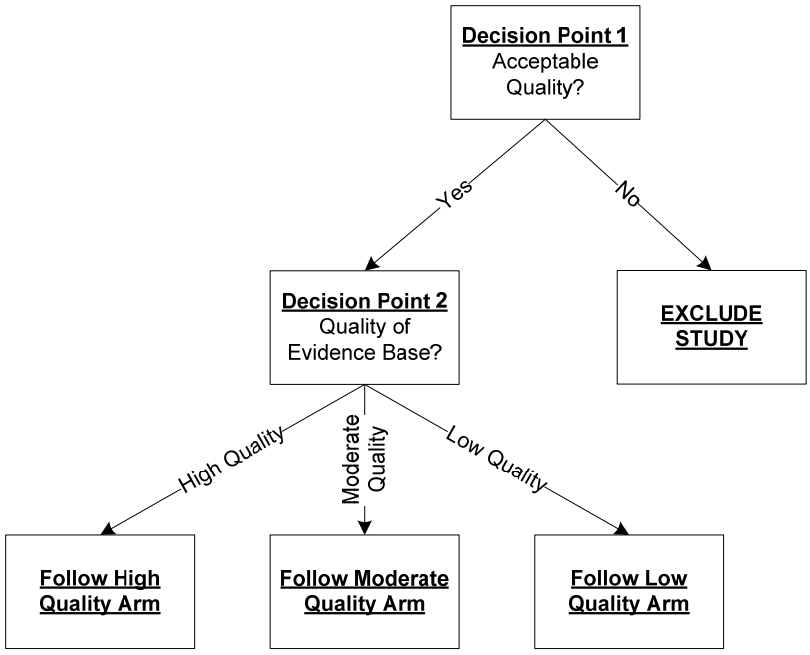


Figure 17. High Internal Validity Arm

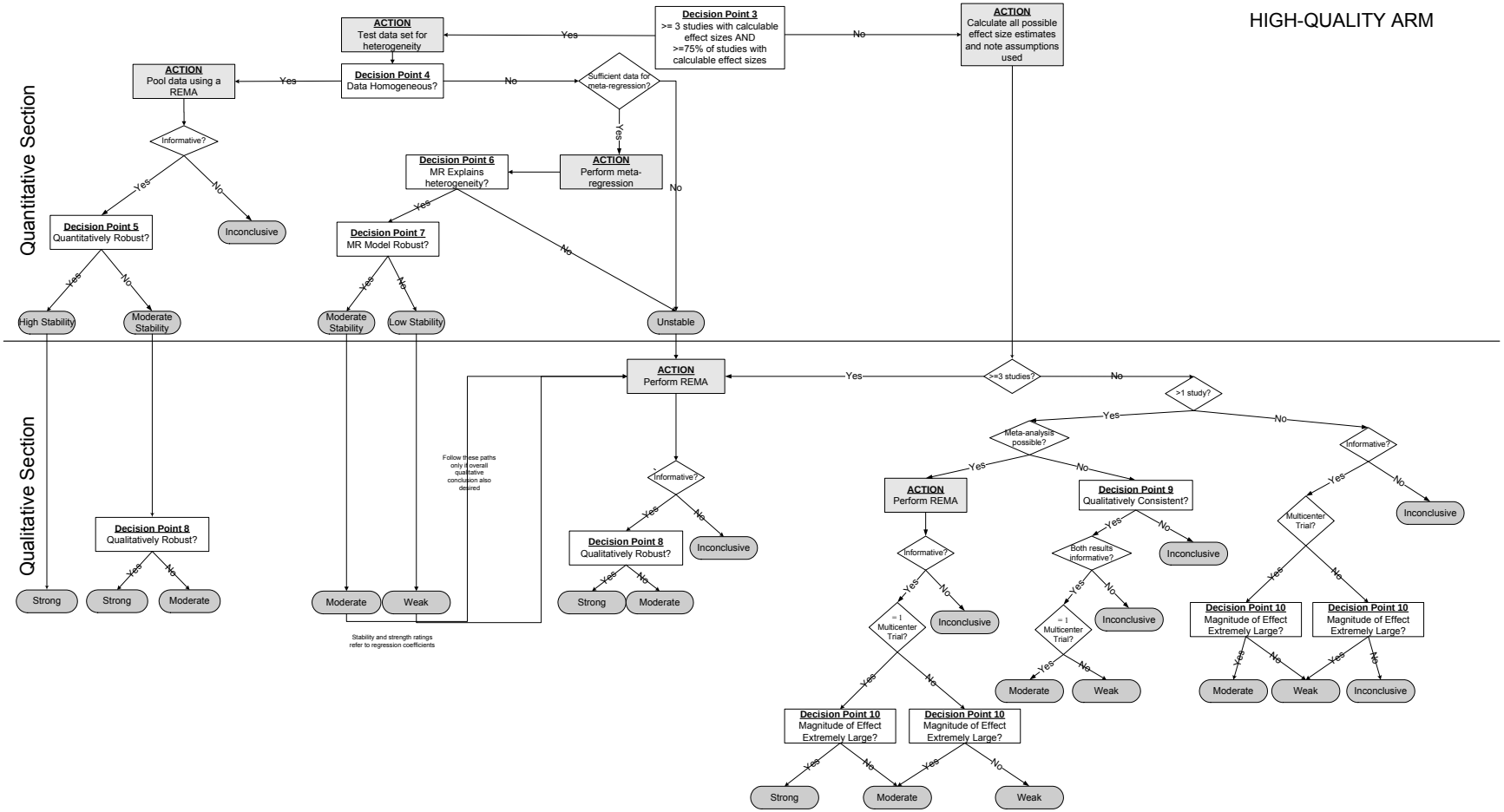


Figure 18. Moderate Internal Validity Arm

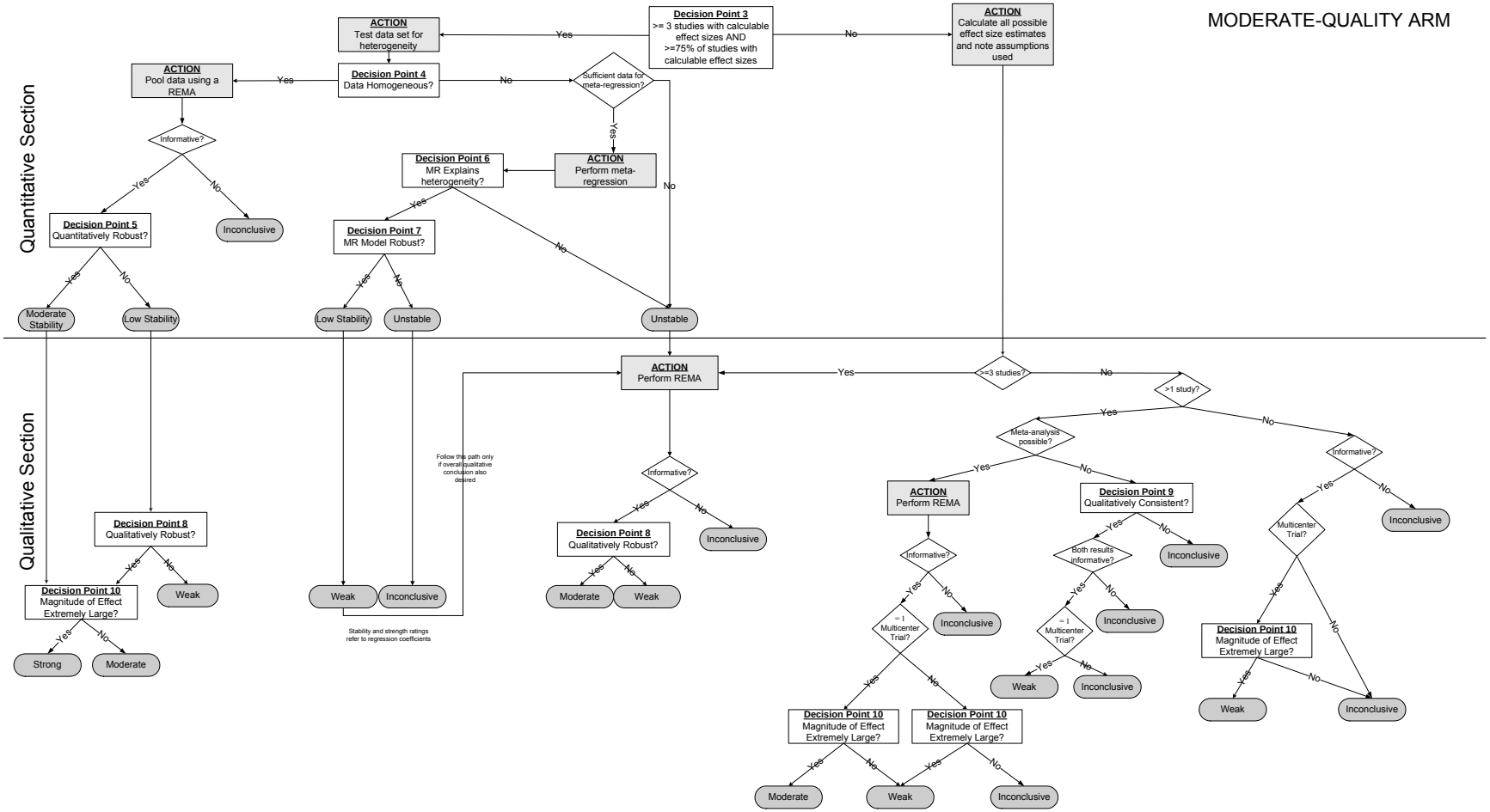
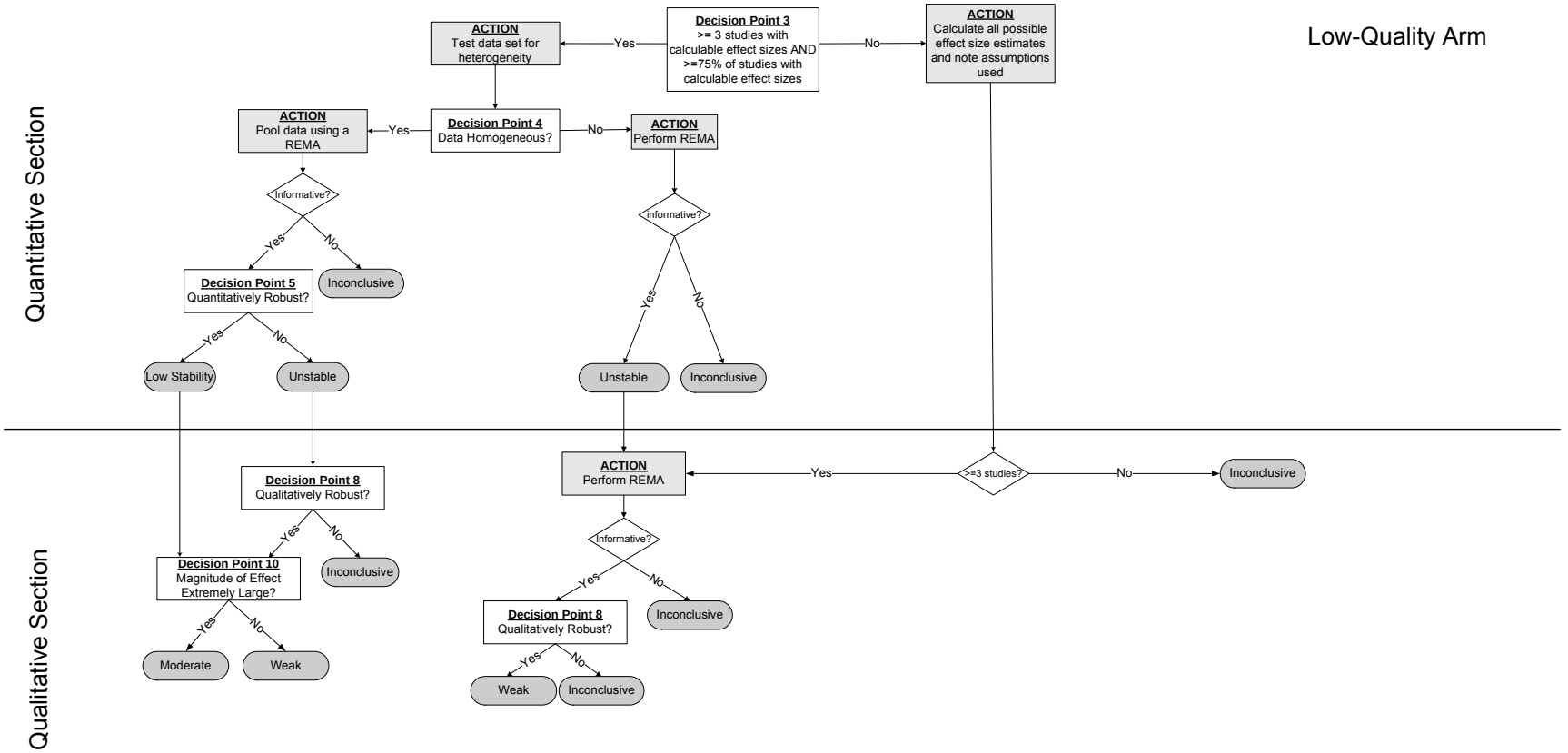


Figure 19. Low Internal Validity Arm



Appendix C. Patient Characteristics and Study Protocols

Table 34. Clinical Study Summary

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Shaladi et al.(71)	2007	Not reported	24	Advanced osteoporosis without recent vertebral fracture VAS >7/10 after 3 months of noninvasive therapies and/including 1 month of systemic (oral and/or transdermal) opioids Treatment-resistant severe side effects to systemic opioids Absence of psychological barriers to treatment success Successful trial of at least 3 days without dramatic dose escalation	Addiction	Vertebral fractures due to osteoporosis	74.3 years (Range: 67 to 83)	79%	1 year	1	Continuous Pain	5.75	Low
										1	≥25% Pain Relief	5.75	Low
										1	≥50% Pain Relief	5.75	Low
										1	Quality of Life	5.75	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA
										2	Adverse Events/Effects	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Deer et al.(70)	2004	166 received trial	136 (82%)	Chronic back pain due to a variety of causes with or without leg pain Only patients with successful trials were implanted	None reported	Back pain due to various causes	55.6 years (Range: 30-83) in trial (30/166 patients were not sub-sequently enrolled)	54% in trial (30/166 patients were not sub-sequently enrolled)	12 months	1	Other Medications and Treatments	NA	NA
										2	Adverse Events/Effects	NA	NA
Thimineur et al.(8)	2004	88 received trial	38 (43%)	Aged 21-75 years No medical or psychological contraindications, including passed psychological evaluation Pain severe and debilitating, Conservative treatments have been exhausted and failed Pain is responsive to opioids, but dose is limited by side effects At least 50% reduction in pain after 3-day inpatient intrathecal	None reported	Not reported	46.1 (±12 years)	Not reported	3 years	1	Employment Status	5.25	Low
										1	Other Medications and Treatments	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
				trial									
Anderson et al.(11)	2003	86; 37 received trial	27 (31% of screened, 73% of trialed)	Chronic nonmalignant pain (lasting at least 6 months) Pain refractory to other medical and/or surgical treatments Sensory loss consistent with anatomic distribution Diagnostic scan consistent with diagnosis No contraindications to surgery Successful intrathecal or epidural trial	Psychopathic and/or substance abuse problems Potential to gain from benefit from lack of improvement	Failed back surgery syndrome (FBSS)	55 years (Range: 32-80)	46%	6 months	1	Continuous Pain Relief	5.0	Low
										1	≥50% Pain Relief	6.0	Low
										1	Discontinuation due to Insufficient Pain Relief	6.0	Low
										1	Functional Status	5.0	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA
										1	Adverse Events/Effects	NA	NA
										4	Cost Issues	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Kumar et al.(68)	2001	25 received trial	16 (64% of trialed)	Severe, chronic, nonmalignant pain refractory to conservative management Known organic benign cause of pain Exclusion of psychiatric or medicolegal issues Successful intrathecal morphine trial	None reported	Various causes	48.1 years (Range: 34-61)	38%	Mean: 29.14 months (SD: 12.44 months), Range: 13 to 49 months	1	Continuous Pain Relief	7.25	Low
										1	≥25% Pain Relief	7.25	Low
										1	≥50% Pain Relief	7.25	Low
										1	Discontinuation due to Insufficient Pain Relief	7.25	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA
										2	Discontinuation due to Adverse Events	7.25	Low
										2	Adverse Events/Effects	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Mironer and Tollison(55)	2001	Not reported	24	Chronic nonmalignant pain resistant to other neuroaxial agents (all patients had failed intrathecal treatment with other agents)	None reported	FBSS	51.5 year (Range: 39 to 70)	62.5%	6 months	1	Continuous Pain Relief	6.5	Low
										1	≥25% Pain Relief	6.5	Low
										1	≥50% Pain Relief	6.5	Low
										1	Quality of Life	6.5	Low
										1	Dose of Infused Medication Over Time	NA	NA
										2	Adverse Events/Effects	NA	NA
Rainov et al.(69)	2001	30 trialed	26 (87% of trialed)	Chronic leg and back pain due to degenerative lumbar spinal disease and at least one failed back surgery Failed conservative physical and pharmacological treatment	Major psychosomatic pain component Unsettled worker's disability claims	FBSS	54 years (Range: 35 to 68)	58%	Mean: 3.5 years, Range: 16 to 38 months	1	Continuous Pain Relief	7.25	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medications over Time	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
				Passed trial intrathecal infusion – no pain change criterion besides patient satisfaction Successful intrathecal trial						2	Adverse Events/Effects	NA	NA
Anderson and Burchiel(6)	1999	40 trialed	30 (75% of trialed)	Severe chronic noncancer pain refractory to less invasive pain control ≥50% pain relief with intraspinal infusion trial	None reported	Nociceptive and neuropathic	58 years	53%	24 months	1	≥25% Pain Relief	6.0	Low
										1	≥50% Pain Relief	6.0	Low
										1	Discontinuation due to Insufficient Pain Relief	6.0	Low
										1	Employment Status	5.0	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
										2	Discontinuation due to Adverse Events	6.0	Low
										2	Adverse Events/Effects	NA	NA
Angel et al.(67)	1998	15 referred, 13 trialed	11 (73% of referred, 85% of trialed)	Chronic nonmalignant pain patients who had failed previous treatment (including surgery) presenting to a neurosurgical clinic	None reported	Failed back syndrome	Mean age not reported, (Range: 29-81)	55%	Median: 28.5 months, up to 3 years	1	Continuous Pain Relief	6.5	Low
										1	≥25% Pain Relief	6.5	Low
										1	≥50% Pain Relief	6.5	Low
										1	Discontinuation due to Insufficient Pain Relief	6.5	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
										2	Discontinuation due to Adverse Events/Effects	6.5	Low
										2	Adverse Events/Effects	NA	NA
Tutak and Doleys(66)	1996	Not reported	26	Chronic noncancer pain Inadequate pain relief with more conservative measure Ineligible for surgical correction of lesions Satisfactory pain relief with 2-3 epidural steroid injections	Significant psycho-pathology, including severe personality disorder or psychosis Inappropriate expectations	Unspecified	44.3 years (Range: 25-62)	35%	Mean: 23 months, Range: 16 to 27 months	1	Employment Status	6.75	Low
										1	Dose of Infused Medication Over Time	NA	NA
										2	Discontinuation due to Adverse Events	NA	NA
										2	Adverse Events/Effects	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Hassenbusch et al.(39)	1995	22 trialed	18 (82% of trialed)	Chronic nonmalignant neuropathic pain Failed/ineligible for noninvasive treatment; no other treatment options available Had at least a 50% reduction of pain on intrathecal trial	Significant psychiatric or personality disorder, including addictive personality, "mental allergy" Morphine or sufentanil citrate allergy Pacemaker Cancer Chronic infection Partial/ complete blockage of spinal canal	Neuropathic	46.6 years (Range: 40-77)	Not reported	Mean: 2.4 years, Range: 0.8 to 4.7 years	1	Continuous Pain Relief	6.5	Low
										1	≥25% Pain Relief	6.5	Low
										1	≥50% Pain Relief	6.5	Low
										1	Discontinuation due to Insufficient Pain Relief	6.5	Low
										1	Other Medications and Treatments	NA	NA
										1	Dose of Infused Medication Over Time	NA	NA
										2	Discontinuation due to Adverse Events/Effects	6.5	Low
										2	Adverse Events/Effects	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Kanoff(7)	1994	Not reported	15	Chronic intractable nonmalignant pain Treated with oral and transdermal opioids and other medications, but with severe breakthrough pain No need for corrective surgery Preimplantation trial introduced later in study, so only 6/15 patients were screened (with both placebo and a spinal opiate) before they received their intrathecal pump	None reported	Mixed	44 years (Range: 28-70)	47%	Mean: 17 months, Range: 2 to 44 months	1	Employment Status	5.25	Low
										1	Other Medications and Treatments	NA	NA
										2	Discontinuation due to Adverse Events/Effects	5.5	Low
										2	Adverse Events/Effects	NA	NA

Study	Year	Number of Patients Screened	Number of Patients Enrolled (% of those screened)	Inclusion Criteria	Exclusion Criteria	Most Common Condition	Age	Gender (% Female)	Duration o f Follow-up	Inclusion for Key Question	Outcome Measure	Internal Validity Score	Internal Validity Category
Krames and Lanning(65)	1993	Not reported – no trial indicated	16	Chronic severe pain from various syndromes Received pump between 2/2/1989 and 12/31/1992 Failure of previous conservative treatments Passed psychological screening	None reported	Mixed	55 years (Range: 32-82)	81%	Mean: 25 months, Range: 5 to 47 months	1	Dose of Infused Medication Over Time	NA	NA
										2	Discontinuation due to Adverse Events/Effects	6.5	Low
										2	Adverse Events/Effects	NA	NA

NA Quality score not applicable for this outcome. See text for explanation (varies by outcome)

Table 35. Patient Enrollment Criteria

Study	Year	Inclusion Criteria	Exclusion Criteria
Shaladi et al.(71)	2007	Advanced osteoporosis without recent vertebral fracture VAS >7/10 after 3 months of noninvasive therapies and/including 1 month of systemic (oral and/or transdermal) opioids Treatment-resistant severe side effects to systemic opioids Absence of psychological barriers to treatment success Successful trial of at least 3 days without dramatic dose escalation	Addiction
Deer et al.(70)	2004	Chronic back pain due to a variety of causes with or without leg pain Only patients with successful trials were implanted	None reported
Thimineur et al.(8)	2004	Aged 21-75 years No medical or psychological contraindications, including passed psychological evaluation Pain severe and debilitating, Conservative treatments have been exhausted and failed Pain is responsive to opioids, but dose is limited by side effects At least 50% reduction in pain after 3-day inpatient intrathecal trial	None reported
Anderson et al.(11)	2003	Chronic nonmalignant pain (lasting at least 6 months) Pain refractory to other medical and/or surgical treatments Sensory loss consistent with anatomic distribution Diagnostic scan consistent with diagnosis No contraindications to surgery Successful intrathecal or epidural trial	Psychopathic and/or substance abuse problems Potential to gain from benefit from lack of improvement
Kumar et al.(68)	2001	Severe, chronic, nonmalignant pain refractory to conservative management Known organic benign cause of pain Exclusion of psychiatric or medicolegal issues Successful intrathecal morphine trial	None reported
Mironer and Tollison(55)	2001	Chronic nonmalignant pain resistant to other neuroaxial agents (all patients had failed intrathecal treatment with other agents)	None reported

Study	Year	Inclusion Criteria	Exclusion Criteria
Rainov et al.(69)	2001	Chronic leg and back pain due to degenerative lumbar spinal disease and at least one failed back surgery Failed conservative physical and pharmacological treatment Passed trial intrathecal infusion – no pain change criterion besides patient satisfaction Successful intrathecal trial	Major psychosomatic pain component Unsettled worker's disability claims
Anderson and Burchiel(6)	1999	Severe chronic noncancer pain refractory to less invasive pain control ≥50% pain relief with intraspinal infusion trial	None reported
Angel et al.(67)	1998	Chronic nonmalignant pain patients who had failed previous treatment (including surgery) presenting to a neurosurgical clinic	None reported
Tutak and Doleys(66)	1996	Chronic noncancer pain Inadequate pain relief with more conservative measure Ineligible for surgical correction of lesions Satisfactory pain relief with 2-3 epidural steroid injections	Significant psychopathology, including severe personality disorder or psychosis Inappropriate expectations
Hassenbusch et al.(39)	1995	Chronic nonmalignant neuropathic pain Failed/ineligible for noninvasive treatment; no other treatment options available Had at least a 50% reduction of pain on intrathecal trial	Significant psychiatric or personality disorder, including addictive personality, "mental allergy" Morphine or sufentanil citrate allergy Pacemaker Cancer Chronic infection Partial/complete blockage of spinal canal
Kanoff(7)	1994	Chronic intractable nonmalignant pain Treated with oral and transdermal opioids and other medications, but with severe breakthrough pain No need for corrective surgery Preimplantation trial introduced later in study, so only 6/15 patients were screened (with both placebo and a spinal opiate) before they received their intrathecal pump	None reported

Study	Year	Inclusion Criteria	Exclusion Criteria
Krames et al.(65)	1993	Chronic severe pain from various syndromes Received pump between 2/2/1989 and 12/31/1992 Failure of previous conservative treatments Passed psychological screening	None reported

Table 36. Patient Characteristics

Study	Year	Most Common Condition	Mean Time Since Onset (Standard Deviation)	Mean Age (Standard Deviation)	Percent Female
Shaladi et al.(71)	2007	Vertebral fractures due to osteoporosis	Not reported, but all patients had to have failed conservative therapy for at least 3 months to meet inclusion criteria	74.3 years (Range: 67 to 83)	79%
Deer et al.(70)	2004	Back pain due to various causes	Not reported	55.6 years (Range: 30-83) in trial (30/166 patients were not subsequently enrolled)	54% in trial (30/166 patients were not subsequently enrolled)
Thimineur et al.(8)	2004	Not reported	6.8 (±4) years	46.1 (±12 years)	Not reported
Anderson et al.(11)	2003	Failed back surgery syndrome (FBSS)	Not reported; at least 6 months to meet inclusion criteria	55 years (Range: 32-80)	46%
Kumar et al.(68)	2001	Various causes	8.0 years (SD 4.2 years)	48.1 years (Range: 34-61)	38%
Mironer and Tollison(55)	2001	FBSS	Not reported	51.5 year (Range: 39 - 70)	62.5%
Rainov et al.(69)	2001	FBSS	19 (±7) months	54 years (Range: 35 to 68)	58%
Anderson and Burchiel(6)	1999	Nociceptive and neuropathic	8 years (Range: 5 to 24 years)	58 years	53%
Angel et al.(67)	1998	Failed back syndrome	Not reported	Mean age not reported, (Range: 29-81)	55%
Tutak and Doleys(66)	1996	Unspecified	115 months (Range: 20 to 360 months)	44.3 years (Range: 25-62)	35%
Hassenbusch et al.(39)	1995	Neuropathic	Not reported	46.6 years (Range: 40-77)	Not reported
Kanoff(7)	1994	Mixed	Not reported	44 years (Range: 28 -70)	47%
Krames et al.(65)	1993	Mixed	Not reported	55 years (Range: 32-82)	81%

Table 37. Study Protocols

Study	Year	Number of Patients Screened	Number of Patients Enrolled	Spinal Drug Efficacy Screening?	Pump	Intrathecally-Administered Drugs	Initial Dose	Final Dose	Adjuvant Treatment	Duration of Treatment
Shaladi et al.(71)	2007	Not reported	24	Yes	Non-programmable constant-flow Archimedes infusion pump (Codman, Johnson & Johnson USA)	Morphine	Mean: 0.33 mg/hr, Range: 0.1 to 0.5 mg/hr	Mean: 0.68 mg/hr, Range: 0.1 to 2.5 mg/hr	No patients received additional oral or transdermal analgesics. Other adjuvants not reported.	1 year
Deer et al.(70)	2004	166 received trial	136 (82%)	Yes, mostly inpatient and with morphine by epidural or intrathecal infusion, mean duration 3.5 days (SD 5.4 days)	Not reported	Morphine	Not reported	Not reported	Systemic opioids allowed	12 months
Thimineur et al.(8)	2004	88 received trial	38 (43%)	Yes, 3-day inpatient intrathecal trial with ≥50% pain relief	Constant flow or programmable pump (Medtronic)	Morphine (n = 9) Hydromorphone (n = 21) Fentanyl (n = 24) Clonidine (n = 23) Baclofen (n = 2) Bupivicaine (n = 1) Methadone (n = 1)	Not reported	Morphine 10.8 mg/d Hydromorphone 13.5 mg/d Fentanyl 664 ug/d Clonidine 378 ug/d Baclofen 120 u/d Bupivicaine 15.0 mg/d Methadone 10.0 mg/d	Adjuvant treatments and medications were permitted. IT pump recipients used fewer drugs, spinal injections, and trigger point injections than a cohort that did not have IT pump	3 years

Study	Year	Number of Patients Screened	Number of Patients Enrolled	Spinal Drug Efficacy Screening?	Pump	Intrathecally-Administered Drugs	Initial Dose	Final Dose	Adjuvant Treatment	Duration of Treatment
Anderson et al.(11)	2003	86; 37 received trial	27 (31% of screened, 73% of trialed)	Yes, by epidural for 36-48 h, or intrathecal infusion for 8-10 h with goal of ≥50% pain relief	Programmable implantable pump (SynchroMed or SynchroMed EL Medtronic Corp.)	Morphine	Initial dose 1 mg/day	4.8 to 48 mg/day	Unspecified non-opioids	6 months
Kumar et al.(68)	2001	25 received trial	16 (64% of trialed)	Yes- details not reported	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Morphine, with clonidine if needed (n = 2)	1.11 mg/day (SD: 1.91 mg/day)	7.42 mg/day (SD: 4.20 mg/day)	10/16 patients used oral antidepressants or analgesics, including oral narcotics in 2 patients for flare pain	Mean: 29.14 months (SD: 12.44 months), Range: 13 to 49 months
Mironer and Tollison(55)	2001	Not reported	24	No – all failed prior IT pump treatment	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Methadone	Mean: 9.2 mg/day (Range: 1.5 to 18)	Mean: 16.8 mg/day (Range: 5 to 36)	Not reported	6 months
Rainov et al.(69)	2001	30 trialed	26 (87% of trialed)	Yes, for 7-10 days	Programmable implantable pump (SynchroMed or SynchroMed EL Medtronic Corp.)	Morphine (n = 24) and/or bupivacaine (n = 20), clonidine (n = 16), or midazolam (n = 10). Patients received morphine plus one or two other drugs.	Test phase as mg/24 hr morphine 0.5(±0.3), midazolam 0.4(±0.2), Clonidine 0.03(±0.015), bupivacaine 1.0(±0.4)	In mg/24 hrs, morphine 5.2(±2.8), bupivacaine 2.5(±1.5), clonidine 0.06(±0.03), midazolam 0.08(±0.4)	Oral opioids and antidepressants discontinued during titration phase, weaned after 3 days of trial	Mean: 3.5 years, Range: 16 to 38 months
Anderson and Burchiel(6)	1999	40 trialed	30 (75% of trialed)	Yes – single intrathecal or epidural infusion	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Morphine	1 mg /day	Up to 25 mg/day	Non-narcotics (all patients) and oral narcotics (30% of patients)	24 months
Angel et al.(67)	1998	15 referred, 13 trialed	11 (73% of referred, 85% of trialed)	No	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Morphine	0.125 to 0.750 mg/day	1.5 to 14.0 mg/day	"Infrequent oral analgesic"	Median: 28.5 months, up to 3 years
Tutak and Doleys(66)	1996	Not reported	26	Yes – epidural infusion for up to 2 weeks	Programmable implantable pump (SynchroMed Model 8615, Medtronic Corp.)	Morphine; 2 switched to fentanyl 14 had tetracaine added, and 2/14 switched from bupivacaine	Not reported	9.34 mg (Range: 1.57 to 61.99 mg) at 21 months	Not reported	Mean: 23 months, Range: 16 to 27 months

Study	Year	Number of Patients Screened	Number of Patients Enrolled	Spinal Drug Efficacy Screening?	Pump	Intrathecally-Administered Drugs	Initial Dose	Final Dose	Adjuvant Treatment	Duration of Treatment
Hassenbusch et al.(39)	1995	22 trialed	18 (82% of trialed)	Yes; 2-5 days. Not placebo-controlled	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Morphine or sufentanil	Morphine (n = 8) mean 0.49(±0.24) mg/hr; Sufentanil (n = 10) mean 0.67(±0.22) ug/hr	Morphine (n = 7) mean 1.11(±0.61) mg/hr, Sufentanil (n = 11) mean 2.39(±0.95) ug/hr	NSAIDS, oral opioids,, acetaminophen, antidepressants, muscle relaxants	Mean: 2.4 years, Range: 0.8 to 4.7 years
Kanoff(7)	1994	Not reported	15	Partial – only last 6/15 patients screened	Programmable implantable pump (SynchroMed, Medtronic Corp.)	Morphine	10 mg/mL to 50 mg/mL per day	Not reported	Not reported	Mean: 17 months, Range: 2 to 44 months
Krames et al.(65)	1993	Not reported – no trial indicated	16	No	Not reported	Morphine and bupivacaine	Morphine 1.7 mg/day (Range: 0.35 to 4.0 mg/day) Bupivacaine 3.71 mg/day (Range: 2.77 to 4.5 mg/day)	Morphine 8.9 mg/day (Range: 0.065 to 18 mg/day) Bupivacaine 4.1 mg/day (Range: 0.19 to 5.8 mg/day)	None reported	Mean: 25 months, Range: 5 to 47 months

Table 38. Prospective and Retrospective Studies

Study	Year	Prospective or Retrospective	How Determined
Shaladi et al.(71)	2007	Not reported	Whether the study was prospectively or retrospectively designed is not explicitly stated. We attempted to contact the following study authors regarding this, but received no response: Ali Shaladi PhD, MD; Maria Rita Saltari, MD; Francesco Crestani, MD
Deer et al.(70)	2004	Prospective	So stated in methods section
Thimineur et al.(8)	2004	Prospective	So stated in materials and methods section
Anderson et al.(11)	2003	Prospective	So stated in title and introduction section of article
Kumar et al.(68)	2001	Prospective	So stated in abstract and introduction. However, some this is somewhat unclear as no institutional review board approval or patient consent is reported, and the letters following article all refer to the study as being retrospective. We attempted to contact the following study authors for clarification, but received no response: Krishna Kumar, MB, MS; Michael Kelly, MD. Although this matter remains unclear, because the authors stated that their study followed patients prospectively, we consider it prospective for the purpose of internal validity assessment.
Mironer and Tollison(55)	2001	Prospective	So stated in abstract
Rainov et al.(69)	2001	Prospective	So stated in methods section
Anderson and Burchiel(6)	1999	Prospective	So stated in title, abstract, and introduction
Angel et al.(67)	1998	Not reported	Whether the study was prospective or retrospective was not clearly stated. We attempted to contact the contact author, Harry J. Gould III MD, PhD, regarding this but received no response. For the purposes of the internal validity assessment, we will consider it 'not reported.'
Tutak and Doleys(66)	1996	Retrospective	Personal communication(173)
Hassenbusch et al.(39)	1995	Prospective	So stated in introduction
Kanoff(7)	1994	Retrospective	Personal communication(174)
Krames et al.(65)	1993	Retrospective	So stated in methods section

Appendix D. Additional Data and Analyses, and Internal Validity Assessments

Pain and Pain Relief

Table 39. Internal Validity Assessment of Continuous Pain Scores

Item		Shaladi et al.(71)	Thimineur et al.(8)	Anderson et al.(11)	Kumar et al.(68)	Mironer and Tollison(55)	Rainov et al.(69)	Anderson and Burchiel(6)	Angel et al.(67)	Hassenbusch et al.(39)
		2007	2004	2003	2001	2001	2001	1999	1998	1995
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	NR*	NR	Yes	Yes	NR	NR	Yes	Yes	NR
4	Was the study prospectively planned?	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No	No	No	Yes	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No	No	No	No	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	NR	No	No	NR	NR	No	No	NR	NR
Individual Study Internal Validity Score		**5.75**	**4.25**	**5.0**	**7.25**	**6.5**	**7.25**	**4.0**	**6.5**	**6.5**
Overall Internal Validity Category (Median Score of Included Studies)		**Low**								

*NR Not reported

Shaded columns excluded from outcome due to unacceptably low internal validity score.

Table 40. Continuous Pain Score Data Sensitivity Analysis: Impact Analysis

Study Removed	N =	Statistics							Standardized Difference in Means and 95% Confidence Interval (CI)	
		Standardized Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	*P*-Value	Pain Scores Lower at Baseline	Pain Scores Lower After Pump Treatment
Hassenbusch et al. 1995(39)	128	2.601	0.555	0.308	1.513	3.689	4.686	<0.001		
Angel et al. 1998(67)	135	2.550	0.529	0.280	1.513	3.588	4.817	<0.001		
Kumar et al. 2001(68)	130	1.994	0.428	0.183	1.155	2.834	4.656	<0.001		
Mironer and Tollison 2001(55)	122	2.719	0.565	0.320	1.610	3.827	4.808	<0.001		
Rainov et al. 2001(69)	120	2.707	0.582	0.339	1.566	3.848	4.650	<0.001		
Anderson et al. 2003(11)	122	2.391	0.517	0.268	1.377	3.404	4.650	<0.001		
Shaladi et al. 2007(71)	122	1.733	0.325	0.105	1.097	2.369	5.342	<0.001		
Summary Effect	146	2.347	0.454	0.206	1.457	3.237	5.167	<0.001		

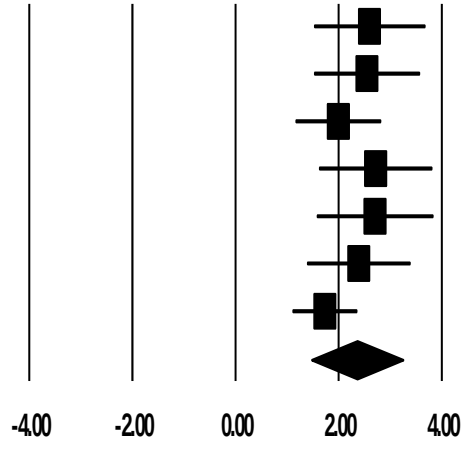


Table 41. Continuous Pain Score Data Sensitivity Analysis: Cumulative Meta-Analysis

Study Added		Statistics							Standardized Difference in Means and 95% Confidence Interval (CI)	
		Standardized Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	P-Value	Pain Scores Lower at Baseline	Pain Scores Lower After Opioid Treatment
Hassenbusch et al. 1995(39)	Total N = 18	1.475	0.341	0.116	0.808	2.143	4.331	<0.001		
Angel et al. 1998(67)	29	1.493	0.270	0.073	0.964	2.023	5.529	<0.001		
Kumar et al. 2001(68)	45	2.334	0.726	0.527	0.911	3.756	3.215	0.001		
Mironer and Tollison 2001(55)	69	2.857	0.492	0.242	0.893	2.821	3.776	<0.001		
Rainov et al. 2001(69)	95	1.598	0.341	0.117	0.929	2.267	4.679	<0.001		
Anderson et al. 2003(11)	119	1.733	0.325	0.105	1.097	2.369	5.342	<0.001		
Shaladi et al. 2007(71)	119	2.347	0.454	0.206	1.457	3.237	5.167	<0.001		
Summary Effect	119	2.347	0.454	0.206	1.457	3.237	5.167	<0.001		

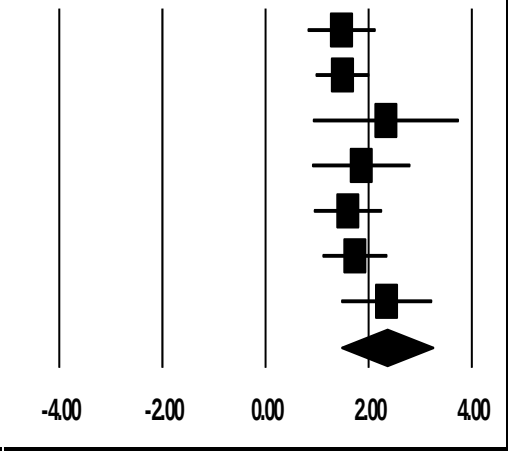


Table 42. Internal validity Assessment of Proportions of Patients Attaining Clinically Significant Pain Relief

Item		Shaladi et al.(71)	Thimineur et al.(8)	Anderson et al.(11)	Kumar et al.(68)	Mironer and Tollison(55)	Rainov et al.(69)	Anderson and Burchiel(6)	Angel et al.(67)	Hassenbusch et al.(39)
		2007	2004	2003	2001	2001	2001	1999	1998	1995
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	NR	NR	Yes	Yes	NR	NR	Yes	Yes	NR
4	Was the study prospectively planned?	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No	No	No	Yes	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No	No	No	No	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	No	No	No	NR	NR	No	No	NR	NR
Individual Study Internal Validity Score		**5.75**	**5.25**	**6.0**	**7.25**	**6.5**	**7.25**	**6.0**	**6.5**	**6.5**
Overall Internal Validity Category of Evidence Base		**Low**								

NR Not reported.

Discontinuation from Clinical Study due to Insufficient Pain Relief

Table 43. Internal Validity Assessment, Discontinuation from Clinical Study due to Insufficient Pain Relief

Item		Anderson et al. 2003(11)	Kumar et al.(68)	Anderson and Burchiel(6)	Angel et al.(67)	Hassenbusch et al.(39)
		2003	2001	1999	1998	1995
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	Yes	Yes	Yes	Yes
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	No	Yes	No	Yes	Yes
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	Yes	Yes	Yes	Yes	NR
4	Was the study prospectively planned?	Yes	Yes	Yes	NR	Yes
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	Yes	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	No	NR	No	NR	NR
Individual Study Internal Validity Score		**6.0**	**7.25**	**6.0**	**6.5**	**6.5**
Overall Internal Validity Score Category of Evidence Base		**Low**				

NR Not reported.

Quality of Life

Table 44. Internal Validity Assessment of Quality of Life

Item	Shaladi et al.(71)	Thimineur et al.(8)	Mironer and Tollison(55)

		2007	2004	2001
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	Yes
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	Yes
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	NR	NR	NR
4	Was the study prospectively planned?	NR	Yes	Yes
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	NR	No	NR
Individual Study Internal Validity Score		**5.75**	**4.25**	**6.5**
Overall Internal Validity Category		**Low**		

NR Not reported.

Shaded study not included in analysis due to unacceptable low internal validity score

Functional Status

Table 45. Internal Validity Assessment, Functional Status

Item		Thimineur et al.(8)	Anderson et al.(11)	Anderson and Burchiel(6)
		2004	2003	1999
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	No	No	No
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	No	No	No
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	NR	Yes	Yes
4	Was the study prospectively planned?	Yes	Yes	Yes
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	No
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	No	NR	No
Individual Study Internal Validity Score		**4.25**	**5.0**	**4.0**
Internal Validity Score Category		**Low**		

NR Not reported.

Employment Status

Table 46. Internal Validity Assessment, Employment Status

Item		Thimineur et al.(8)	Anderson and Burchiel(6)	Tutak and Doleys(66)	Kanoff(7)
		2004	1999	1996	1994
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	No	No	Yes	No
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	No	No	Yes	No
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	NR	Yes	NR	NR
4	Was the study prospectively planned?	Yes	Yes	No	No
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No	No
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	Yes	Yes	Yes	Yes
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	No	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	No	No	No	No
Individual Study Internal Validity Score		**5.25**	**5.0**	**6.75**	**5.25**
Internal Validity Score Category		**Low**			

NR Not reported.

Use of Other Medications and Treatments

Table 47. Use of Other Medications and Treatments

Study	Year	Adjunctive Treatments Allowed?	Adjunctive Treatment Use at Follow-up	Bottom Line: Did Use of Other Medications Decrease Overall?
Kanoff(7)	1994	Yes	3/15 patients used oral opioids occasionally (n = 2) or at bedtime (n = 1) 1/15 patients took Prozac and Xanax	Yes

Study	Year	Adjunctive Treatments Allowed?	Adjunctive Treatment Use at Follow-up	Bottom Line: Did Use of Other Medications Decrease Overall?
Hassenbusch(39)	1995	Yes	13/18 took oral opioids at follow up, compared with 15/18 at baseline. Dosage change cannot be analyzed because preoperative dosages not reported 10/18 took non-opioids (e.g., acetaminophen, muscle relaxants, antidepressants) at follow-up, vs. 15/18 preoperative	Yes
Angel et al.(67)	1998	Yes	Authors reported that "all patients required infrequent oral analgesic supplementation."	Yes
Anderson and Burchiel(6)	1999	Yes	Intake not quantified 28/30 (93%) took systemic narcotics regularly at baseline, and 6/20 (30%) did at 24 months follow up 14/20 (70%) did not use any other narcotics No significant change in non-narcotics from baseline to follow up	Yes
Rainov et al.(69)	2001	No – Patients were tapered off	---	Yes
Anderson et al.(11)	2003	Yes	Medication Quantification Scale (MQS) scores decreased significantly after 6 months, from 29 (±14 SD) to 12 (±10 SD) ($P < 0.001$) As assessed by MQS, non-opioid systemic medication intake was not significantly different ($P = 0.31$) before and after pump implantation	Yes
Kumar et al.(68)	2001	Yes	10/16 patients continued use of systemic antidepressants or analgesics after pump implantation. Two patients used oral narcotics for acute flares. Before implantation, all patients took systemic medications.	Yes
Deer et al.(70)	2004	Yes	65% of patients decreased use of systemic opioids from baseline by 6 months of treatment 47% of patients decreased systemic opioids use at 12 months compared to 6 months	Yes

Study	Year	Adjunctive Treatments Allowed?	Adjunctive Treatment Use at Follow-up	Bottom Line: Did Use of Other Medications Decrease Overall?
Thimineur et al.(8)	2004	Yes	Pump recipients took an average of 794 (±645 SD) mg oral morphine at baseline, and 388mg (±659) at 36 months Controls who did not receive a pump took an average of 582 (±660) mg oral morphine at baseline, compared with 952 (±982 SD) at 36 months Pump recipients used an average of 55 (±76 ug SD) transdermal fentanyl at baseline and 20 ug (±44 SD) at 36 months Controls who did not receive a pump used an average of 18 ug (±44 SD) transdermal fentanyl at baseline and 38 (±85 SD) at 36 months During the course of the study pump recipients (n = 38) had 44 spinal injections in 15 patients and 45 trigger point injections in 15 patients Non-recipients (n = 31) had 68 spinal injections in 14 patients and 321 trigger point injections in 19 patients	Yes
Shaladi et al. 2007(71)	2007	Yes	All patients were on systemic narcotics at baseline, including 2 that received epidural morphine At 1 year, the authors report that no patients required oral or transdermal analgesics	Yes

Table 48. Daily Dosage Over Time

Study	Year	Initial (SD*)	N =	6 months (SD)	n =	9 months (SD)	n =	12 months (SD)	n =	15 months (SD)	n =	18 months (SD)	n =	21 months (SD)	n =	24 months (SD)	N =	28-29 months (SD)	N =	36 months (SD)	N =
Morphine or Morphine Equivalent/Equianalgesic Dose (mg)																					
Shaladi et al.(71)	2007	7.92 (2.88)	24	-	-	-	-	16.32 (2.88)	-	-	-	-	-	-	-	-	-	-	-	-	-
Anderson et al.(11)	2003	0.87 (0.38)	24	4.1 (2.7)	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kumar et al.(68)	2001	1.11 (1.91)	16	3.10 (3.24)	16	-	-	-	-	-	-	-	-	-	-	-	-	7.42 (4.20)	12	-	-
Rainov et al.(69)	2001	1.21	26	2.65	26	3.33	26	3.85	26	4.04	26	4.56	26	4.96	26	5.23	26	-	-	-	-
Anderson and Burchiel(6)	1999	1.99 (1.75)	30	-	-	-	-	-	-	-	-	-	-	-	-	14.59 (20.52)	23	-	-	-	-
Angel et al.(67)	1998	0.47 (0.37)	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.6 (4.6)	11
Tutak and Doleys(66)	1996	1.38 (R 0.48-6.09)	26	2.47 (R 0.38-6.53)	26	3.67 (R 1.03-4.36)	26	5.49 (R 1.11-40.16)	26	7.48 (R 1.30)	26	8.79 (R 1.40-76.30)	26	9.34 (1.57-61.99)	26	-	-	-	-	-	-
Hassenbusch et al.(39)	1995	14.1 (SEM† 1.3)																45.1 (SEM 5.7)			
Krames et al.(65)	1993	1.7 (R** 0.35-4.0)	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8.9 (R 0.065-18.0)	16	-	-

Study	Year	Initial (SD*)	N =	6 months (SD)	n =	9 months (SD)	n =	12 months (SD)	n =	15 months (SD)	n =	18 months (SD)	n =	21 months (SD)	n =	24 months (SD)	N =	28-29 months (SD)	N =	36 months (SD)	N =
Methadone (mg)																					
Mironer and Tollison(55)	2001	9.21 (4.65)	24	16.77 (6.95)	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sufentanil (ug)																					
Hassenbusch et al.(39)	1995	18.24	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	57.36 (22.8)	11	-	-

* SD: Standard deviation
** R: Range
† SEM: Standard error of the mean

Appendix E. Adverse Events and Discontinuation from Clinical Study due to Adverse Events

Discontinuation from Trial due to Adverse Events

Table 49. Internal validity Assessment on Discontinuation from Clinical Study due to Adverse Events

Item		Kumar et al.(68)	Anderson and Burchiel(6)	Angel et al.(67)	Tutak and Doleys(66)	Hassenbusch et al.(39)	Kanoff(7)	Krames & Lanning(65)
		2001	1999	1998	1996	1995	1994	1993
1	For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patient who completed the study to the timepoint of interest?	Yes	No	Yes	Yes	Yes	Yes	Yes
3	Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?	Yes	Yes	Yes	NR	NR	NR	Yes
4	Was the study prospectively planned?	Yes	Yes	NR	NR	Yes	No	No
5	Did ≤5% of patients receive ancillary treatment(s)?	No	No	No	No	No	NR	NR
6	Was compliance with treatment ≥85%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Was the outcome measure of interest objective and was it objectively measured?	No	No	No	No	No	No	No
8	Was a standard instrument used to measure the outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Did ≥85% of the patients contribute data to this outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was the funding for this study derived from a source that would not benefit financially from results in a particular direction?	NR	No	NR	No	NR	No	NR
Individual Study Internal Validity Score		**7.25**	**6.0**	**6.5**	**5.25**	**6.5**	**5.5**	**6.5**
Internal Validity Category		**Low**						

NR Not reported.

Adverse Events

Table 50. Opioid-related Adverse Events in Case Series

Study	Krames et al.(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel†(11) 2003	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson etl al.(6) 1999	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	18	26	11	30	16	24	26	24	44	24
Addiction/Dependence	NR	NR	0 (0%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Amenorrhea	3 (19%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Arthralgia	3 (19%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Asthma Provocation	NR	2 (15%)	NR	NR	NR	NR	3 (19%)	NR	NR	NR	NR	NR
Blurred Vision	NR	NR	NR	NR	NR	NR	NR	1 (4%)	NR	NR	NR	NR
Constipation	NR	NR	NR	NR	NR	9 (31%)	10 (63%)	NR	NR	14 (38%)	NR	NR
Death	NR	NR	NR	NR	0 (0%)	NR	NR	NR	NR	NR	3 (6.8%)*	NR
Depression	NR	NR	NR	NR	NR	NR	8 (50%)	NR	NR	NR	NR	NR
Diaphoresis	NR	NR	NR	NR	NR	3 (10%)	NR	NR	NR	13 (54%)	NR	NR

Study	Krames et al.(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel†(11) 2003	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson etl al.(6) 1999	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	18	26	11	30	16	24	26	24	44	24
Diarrhea, severe	1 (6%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dizziness	NR	NR	NR	NR	NR	NR	10 (63%)	NR	NR	NR	NR	NR
Hallucinations	NR	NR	NR	NR	NR	NR	4 (25%)	NR	NR	NR	NR	NR
Hypotension	NR	1 (7%)	NR	NR	NR	6 (16%)	NR	NR	NR	NR	NR	NR
Insomnia	NR	NR	NR	NR	NR	NR	4 (25%)	NR	NR	7 (30%)	NR	NR
Leg swelling/Edema (Mild)	NR	NR	3 (27%)	NR	NR	NR	8 (50%)	NR	NR	NR	NR	NR
Lethargy/Fatigue	NR	NR	NR	NR	NR	NR	12 (78%)	NR	NR	4 (14%)	NR	NR
Loss of Appetite	NR	NR	NR	NR	NR	NR	10 (63%)	NR	NR	NR	NR	NR
Mental Status Change, Confusion, Cognitive change	NR	NR	0 (0%)	NR	NR	7 (23%)	NR	NR	NR	10 (40%)	NR	NR
Motor/Sensory Function Loss	NR	NR	NR	NR	0 (0%)	NR	NR	NR	NR	NR	NR	NR

Study	Krames et al.(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel†(11) 2003	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson etl al.(6) 1999	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	18	26	11	30	16	24	26	24	44	24
Myoclonic jerk/spasm	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nausea of Nausea/Vomiting	NR	NR	NR	3 (12%)	3 (27%)	6 (21%)	8 (50%)	NR	NR	10 (40%)	NR	3 (12.5%) (trial)
Nightmares	NR	NR	NR	NR	NR	NR	6 (38%)	NR	NR	NR	NR	NR
Peripheral edema	NR	NR	NR	NR	NR	1 (3%)	NR	NR	NR	NR	NR	NR
Pruritus	NR	NR	NR	4 (15%)	2 (18%)	4 (14%)	9 (55%)	NR	NR	4 (14%)	NR	3 (12.5%) (trial)
Respiratory Depression	NR	NR	0 (0%)	NR	0 (0%)	NR	NR	NR	NR	NR	NR	NR
Sedation	NR	NR	0 (0%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sexual Disturbance: Decreased Libido	NR	NR	NR	1 (4%)	NR	NR	6 (38%)	NR	NR	NR	NR	NR
Sexual Disturbance: Potency	NR	2 (10%)	NR	NR	NR	NR	2 (13%)	NR	NR	NR	NR	NR

Study	Krames et al.(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel†(11) 2003	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson etl al.(6) 1999	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	18	26	11	30	16	24	26	24	44	24
Sweating, Increased	NR	NR	NR	1 (4%)	NR	NR	11 (69%)	NR	NR	NR	NR	NR
Tolerance	NR	NR	NR	NR	NR	7 (30%)	NR	NR	NR	NR	NR	NR
Urinary Disturbance	NR	NR	3 (27%)‡	NR	NR	NR	10 (63%)	NR	NR	NR	NR	NR
Urinary Hesitancy	NR	NR	NR	NR	NR	1 (3%)	NR	NR	NR	17 (55%)	NR	NR
Urinary Retention	NR	2 (13%)	4 (36%)	2 (8%)	2 (18%)	14 (38%)	NR	NR	NR	NR	NR	NR
Vomiting	NR	NR	NR	NR	NR	7 (19%)	NR	NR	NR	NR	NR	5 (21%) (trial)
Weakness	NR	NR	NR	1 (4%)	NR	NR	NR	NR	0 (0%)	NR	NR	NR

* Due to 1 suicide, 1 myocardia infarction, and 1 unknown cause; Not clear whether these were actually opioid-related
† At three months
‡ Worsening of bladder control
NR Not reported.

Table 51. Data on Addiction from Case Series

Study	Year	Patients Screened for Addiction Before Enrollment	Number of Patients Enrolled	Number of Cases of Addiction Observed	Definition of Addiction Used
Krames and Lanning(65)	1993	Not Reported	16	Not Reported	Not Reported
Kanoff(7)	1994	Not Reported	15	Not Reported	Not Reported
Hassenbusch et al.(39)	1995	✓	18	0	Not Reported
Tutak and Doleys(66)	1996	✓	26	Not Reported	Not Reported
Angel et al.(67)	1998	Not Reported	11	Not Reported	Not Reported
Anderson and Buchiel(6)	1999	✓	30	1	Drug-Seeking Behavior
Kumar et al. 2001(68)	2001	Not Reported	16	Not Reported	Not Reported
Mironer and Tollison(55)	2001	Not Reported	24	Not Reported	Not Reported
Rainov et al.(69)	2001	Not Reported	26	Not Reported	Not Reported
Anderson et al.(11)	2003	✓	27	Not Reported	Not Reported
Thimineur et al.(8)	2004	Not Reported	44	Not Reported	Not Reported
Shaladi et al.(71)	2007	✓	24	Not Reported	Not Reported

Table 52. Device-related Adverse Events in Case Series

Study	Krames and Lanning(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel(6) 1999	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson et al.(11) 2003	Deer et al.(70) 2004	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	22	26	11	25	16	24	26	18	136	44	24
Battery depletion	NR	NR	2 (9%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Catheter dislocation requiring reinsertion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		NR	2 (8%)
Catheter-related not requiring re-operation	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (2.3%)	NR
Catheter-related requiring re-operation	2 (13%)	2 (13%)	5 (23%)	9 (35%)	0 (0%)	5 (20%)	1 (6%)	NR	2 (12%)	NR	2 (1.5%)	1 (2.3%)	NR
Cerebrospinal fluid hygroma, self-limiting	1 (6%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cerebrospinal fluid leak	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (0.7%)	NR	NR
Delayed healing	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (4%)
Infection	NR	0 (0%)	NR	NR	0 (0%)	0 (0%)	1 (6%)	NR	NR	NR	3 (2.2%)	2 (5%)	1 (4%)
Infection requiring reoperation and replacement after treatment of infection	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (4.5%)	NR
Local pain at pump site	NR	1 (7%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mild swelling and/or pain at surgical site	NR	1 (7%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study	Krames and Lanning(65)	Kanoff(7)	Hassenbusch et al.(39)	Tutak and Doleys(66)	Angel et al.(67)	Anderson and Burchiel(6)	Kumar et al.(68)	Mironer and Tollison(55)	Rainov et al.(69)	Anderson et al.(11)	Deer et al.(70)	Thimineur et al.(8)	Shaladi et al.(71)
	1993	1994	1995	1996	1998	1999	2001	2001	2001	2003	2004	2004	2007
n =	16	15	22	26	11	25	16	24	26	18	136	44	24
Number of patients re-operation required (any reason)†	3 (19%)	2 (13%)	6 (27%)	11 (42%)	1 (9%)	5 (20%)	4 (25%)	NR	3 (11.5%)	NR	21 (15%)	4 (9%)	NR
Perioperative Complications Requiring Surgical Intervention	NR	NR	NR	NR	NR	0 (0%)	NR	NR	NR	NR	2 (1.5%)	NR	NR
Post-dural puncture spinal headache	5 (31%)	NR	NR	NR	0 (0%)	2 (1%)	NR	NR	NR	NR	NR	NR	NR
Pump malfunction or failure requiring surgical intervention	1 (6%)	0 (0%)	1 (5%)	NR	0 (0%)	2 (8%)	1 (6%)	NR	1 (6%)	NR	NR	NR	NR
Pump mal-position requiring surgical intervention	NR	0 (0%)	2 (9%)	1 (4%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pump programming malfunction	NR	0 (0%)	NR	NR	NR	1 (4%)	NR	NR	NR	NR	NR	NR	NR
Seroma at pump pocket site	1 (6%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Spinal root irritation with radiculitis, temporary	1 (6%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Surgical difficulty	NR	NR	NR	NR	NR	NR	NR	NR	NR	3 (18%)	NR	NR	NR

Study	Krames and Lanning(65) 1993	Kanoff(7) 1994	Hassenbusch et al.(39) 1995	Tutak and Doleys(66) 1996	Angel et al.(67) 1998	Anderson and Burchiel(6) 1999	Kumar et al.(68) 2001	Mironer and Tollison(55) 2001	Rainov et al.(69) 2001	Anderson et al.(11) 2003	Deer et al.(70) 2004	Thimineur et al.(8) 2004	Shaladi et al.(71) 2007
n =	16	15	22	26	11	25	16	24	26	18	136	44	24
Dislodgement/ displacement (unclear if refers to pump or catheter)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (1.5%)	NR	NR

† Five patients had seven complications requiring five re-operations.

NR Not reported.

Table 53. MAUDE Adverse Event Reports for Implantable Pumps 1996-February 2008: Serious Adverse Events

Adverse Event	Number of Reports
Patient Health Outcome	
Infection	128
Inflammatory mass(es)	83
Death	53
Respiratory difficulties	28
Overdose	24
Severe Paralysis	20
Perioperative implantation complication	19
Unresponsive	19
Lethargy/slurred speech	17
Total lack of effect	14
Altered mental status	12
Confusion	10
Coma	9
Loss of consciousness	8
Seizure	7
Hypertension	6
Reduced consciousness	6
Respiratory arrest	6
Pneumonia	5
Tachycardia	5
Severe Peripheral Edema	4
Apneic	3
Bradycardia	3
Cyanosis	3
Hypotension	3
Obtunded	3
Shakiness	3
Cardiopulmonary arrest	2
Hypoxic injury	2
Severe spinal stenosis	2
Stroke	2
Stupor	2
Syncope	2

Adverse Event	Number of Reports
Transverse myelitis	2
Alternating episodes of sedation and withdrawal	1
Arrhythmia	1
Autonomic dysreflexia symptoms	1
Brain stem infarct	1
Cellulitis	1
Chest discomfort	1
Circulatory shock	1
Drug toxicity	1
Kidney failure	1
Mini stroke	1
Multi-organ failure	1
Myocardial infarction	1
Neurological deficit	1
Opioid toxicity	1
Peritonitis	1
Pleural effusion	1
Rhabdomyolysis	1
Ruptured peptic ulcer	1
Sepsis	1
Septic shock	1
Type I diabetes	1
Device-Related Event	
Re-operation due to pump or catheter failure	405
Removal of device (no replacement)	211
Revision or repair but not reoperation due to pump or catheter failure (includes catheter coming out of intrathecal space)	86
Operator error (i.e., pump fill, programmed incorrectly)	35
Pump stopped (no removal/revision)	28
Planned device replacement (battery replacement)	26
Pump programming malfunction	10
Surgical error	5
Malformation of cassette valve seat	1

Table 54. MAUDE Adverse Event Reports for Implantable Pumps 1996-February 2008: Deaths

Adverse Event	Number of Reports
Cause of Death	
Unknown (5 pts died w/in 24 hrs of catheter revision/ pump replacement, 1 pt died w/in 48 hrs, 2 pts died after pump refill/reprogram)	15
Cardio/pulmonary arrest	7
Cardiac disease	5
Overdose	5
Epileptic seizure	4
Pneumonia	4
Disease progression	3
Pump malfunction	2
Unknown – not due to pump	2
Brain hemorrhage	1
Multi-organ failure	1
Multiple spinal puncture wounds	1
Self medication	1
Sepsis	1
Use of Dilaudid in pump	1
TOTAL	**53**

Table 55. MAUDE Adverse Event Reports for Implantable Pumps 1996-February 2008: Miscellaneous Adverse Events

Miscellaneous Adverse Events	Number of Reports
Increased spasticity	46
Numbness – leg/feet	33
Nausea	21
Itchiness	20
Vomiting	20
Withdrawal symptoms	20
Increased pain	19
Bladder/bowel complications	17
Sleepiness	13
Fever	12
Headaches	12
Uncontrolled pain	12
Hypertonia	11
Acne/swelling/redness near catheter site	8
Back discomfort	7
Diaphoresis	7
Diarrhea	7
Gastrointestinal complications	6
Irritability	6
Weakness	6
Severe spasticity	5
Visual disturbances	5
Dizziness	4
Sweating	4
Tremors	4
Anxiety	3
Chills	3
Flaccidity	3
Numbness – arm	3
Edema	2
Flushing	2
Hallucinations	2
Hypotonia	2
Loss of memory	2

Miscellaneous Adverse Events	Number of Reports
Malaise	2
Rigidity	2
Tingling	2
Unable to sleep	2
Abdominal spasms	1
Anorexia	1
Ataxia	1
Bad taste/mouth	1
Burning skin	1
Cerebrospinal fluid leak	1
Cold sweats	1
Cough	1
Decreased cognitive function	1
Dehydration	1
Depression	1
Difficulty swallowing	1
Disabling pain	1
Drooling	1
Dysreflexia	1
Dystonia	1
Falling	1
Felt String/Food on Teeth	1
Fungal infection	1
Genitofemoral ilioinguinal nerve compression	1
Hip discomfort	1
Hot flashes	1
Hypoglycemia	1
Hypokalemia	1
Hypothermia	1
Kidney pain	1
Latex allergy	1
Lip droop	1
Loss of muscle strength	1
Lumbar radicular pain	1
Mild yawning	1
Mood changes	1

Miscellaneous Adverse Events	Number of Reports
Muscle atrophy	1
Mydriasis	1
Night sweats	1
Numbness – saddle distribution	1
Pelvic pain	1
Rash	1
Restlessness	1
Ringing	1
Sensory deficits	1
Seroma	1
Spasms (lower extremities)	1
Spinal cord spasticity	1
Swelling (waistline and between legs)	1
Weight loss	1