Systematic Review of Intrathecal Infusion Systems for Long-Term Management of Chronic Non-Cancer Pain

Vikram B. Patel, MD1, Laxmaiah Manchikanti, MD2, Vijay Singh, MD3, David M. Schultz, MD4, Salim M. Hayek, MD, PhD5, and Howard S. Smith, MD6

Background: Disability, societal, and health impact of chronic intractable pain secondary to various failed therapies is a major issue. As advanced therapy, implantable therapies, which include intrathecal devices and spinal cord stimulation systems, are frequently used in managing chronic intractable pain. Thus, continuous infusion of intrathecal medication is one of the methods used for the control of chronic, refractory, cancer, and non-cancer pain. However, despite the high costs of chronic non-cancer pain, it has been claimed that there is a lack of evidence for intrathecal infusion systems and the cost effectiveness of these systems has been questioned in improving pain and function.


Objective: To determine the efficacy, utilization, safety, and complications associated with the use of intrathecal infusion devices for long-term management of chronic non-cancer pain.

Methods: Literature search was performed through EMBASE, Medline, Cochrane databases, and systematic reviews identified from 1966 to December 2008. Studies were then reviewed and assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies and the Cochrane Musculoskeletal Review Group criteria for randomized trials.

The level of evidence was determined using 5 levels of evidence, ranging from Level I to III with 3 subcategories in Level II, based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

Outcome Measures: The primary outcome measure was pain relief (short-term relief ≤ one-year and long-term > one-year). Secondary outcome measures of improvement in functional status, psychological status, return to work, and reduction in opioid intake were also utilized.

Results: The level of evidence for intrathecal infusion systems indicated either Level II-3 or Level III (limited) based on U.S. Preventive Services Task Force (USPSTF) criteria.

Limitations: The limitations of this study include the paucity of literature, lack of quality evidence, and lack of randomized trials.

Conclusion: This systematic review illustrates Level II-3 or Level III (limited) evidence for intrathecal infusion systems for long-term relief in chronic non-cancer pain.

Key words: Intrathecal infusion, intraspinal infusion, programmable infusion systems, spinal infusion, intra-spinal infusion devices, baclofen infusion, intrathecal opiates

Pain Physician 2009; 12:345-360
Spinal pain is associated with significant economic, societal, and health impact (1-16). Estimates and patterns of direct health care expenditures among individuals with back pain in the United States reached $90.7 billion for the year 1998 (3). In the United States, it was estimated that the cost of treatment in the first year after failed back surgery for pain was approximately $18,883 in 1997 (4). In addition to this, annual health care costs incurred by chronic pain patients, excluding cost for surgical procedures, may range from as low as $500.00 to as high as $35,400 (4,5). Deyo et al (9) showed that the prevalence of chronic back pain and its impact has spawned a rapidly expanding range of tests and treatments, with wide usage for indications that are not well validated, leading to uncertainty about efficacy and safety, increasing complication rates, and marketing abuses. They also showed that the limited studies available suggest that these increases have not been accompanied by population-level improvements in patient outcomes or disability rates. Asche et al (8) reviewed low back pain studies with economic implications in order to determine whether the societal costs attributed to lower back pain have changed since 2001, a time during which low back pain treatment guidelines were updated. They concluded that cost estimates for the management of low back pain were high, consistent with the results of the review of low back pain economic studies published prior to 2001. Newer, more costly agents will increase drug costs as a portion of total cost, particularly if not used in accordance with treatment guidelines.

Stewart et al (15) in an evaluation of low productive time (LPT) and cost due to common pain conditions in the U.S. work force concluded that pain is an inordinately common and disabling condition in the U.S. work force, with most of the pain-related LPT occurring while employees are at work resulting in reduced performance. Martin et al (16) in a review of expenditures and health status among adults with back and neck problems in the United States concluded that self-reported back and neck problems accounted for a large portion of health care expenditures, with spine-related expenditures increasing substantially from 1997 to 2005, without evidence of corresponding improvements in self-assessed health status. Further, studies have shown the rising prevalence of chronic low back pain (2).

Failed back surgery syndrome is a common problem in the modern world, specifically in the United States (17-21). Recent literature about the utilization of surgical interventions in the United States shows that in the year 2002, more than one million spinal procedures were performed with 400,000 cases being instrumented (22-26). Management of failed back surgery syndrome with multiple modalities, including interventional techniques, results in moderate improvements, yet leaves a proportion of patients in intractable pain (1,27-38).

As an advanced stage intervention, implantable therapies, which include spinal cord stimulation systems and implantable intrathecal devices, are frequently used in managing chronic intractable pain. Thus, continuous infusion of intrathecal medication is one of the methods used for control of chronic, refractory, malignant, and non-cancer related pain. However, along with costs of inpatient surgery, expenses for implantable therapy have increased substantially in the entire population and specifically in the Medicare population (39-43). Thus, given the high cost of intrathecal implantables and lack of demonstrated effectiveness, there has been substantial controversy with the usage of intrathecal infusion systems (44-48).

Bennett et al (49) concluded that clinical efficiency in large-scale randomized controlled trials (RCTs) utilizing intrathecal delivery of most compounds has not been demonstrated and variations between study designs make useful comparisons of existing studies difficult. Walker et al (50) concluded that the evidence for the safety and effectiveness of combination spinal analgesic therapies is moderate in acute pain, whereas, they found limited or no evidence to support the combination analgesics in chronic pain. Turner et al (51), in a systemic review of effectiveness and complications of programable intrathecal opioid delivery systems for chronic non-cancer pain, included 6 studies in the evidence synthesis and found improvement in pain among patients who received a permanent intrathecal drug delivery system (52-57). Boswell et al (1) concluded that there is moderate evidence for long-term management of chronic pain with intrathecal infusion systems at one year or longer follow-up. Manchikanti et al (48) in a reassessment of an evidence synthesis by the American College of Occupational and Environmental Medicine (ACOEM) guidelines also found moderate evidence for long-term management of chronic non-cancer pain with intrathecal infusion systems. In addition, a cost effectiveness evaluation showed intrathecal morphine delivery resulting in low cumulative 60-month...
Intrethecal Infusion Systems for Chronic Non-Cancer Pain

costs of $16,579 per year, $1,382 per month versus medical management of $17,037 per year, $1,420 per month (58). Cost effectiveness was also shown with a total cost of intrathecal morphine over 60 months of $82,893, an average of $1,382 per month (5). However, due to all the randomized trials evaluating only short-term relief, the evidence has been shown to be limited in other guidelines (44-48).

This systematic review is undertaken to provide a comprehensive and systematic review of the available literature on intrathecal implantables in managing chronic non-cancer pain.

**METHODS**

**Literature Search**

A literature search was conducted from 1966 through December 2008 using multiple sources including Medline and EMBASE databases, the Cochrane library, systematic and narrative reviews, NIH Clinical Trials Registry, and bibliographic references. Only English language articles were screened.

The search terminology included implantable infusion (drug delivery systems), intrathecal, infusion of morphine, bupivacaine, clonidine, hydromorphone, baclofen, ziconotide, chronic pain, chronic low back pain and chronic non-cancer pain, failed back surgery syndrome, post-surgery syndrome, and arachnoiditis.

**Selection Criteria**

The studies included in this review had to meet the following criteria:

- Studies should clearly show the use of intrathecal infusion device/system (programmable or fixed infusion rate) implanted for non-cancer pain for long-term use.
- Studies must have a specific indication for intrathecal infusion and the drug injected.
- A minimum of 12 months of follow-up was available.
- Clear documentation of patient outcomes and complications should have been provided.
- Number of patients evaluated must be at least 25.

Exclusion criteria were as follows:

- Lack of clear documentation of infusion systems or mixed delivery methods.
- Externalized infusion systems for short-term use.
- Studies for non-cancer pain with less than 12 months follow-up.

- Lack of clear documentation of the indications and patient population being studied.

**Types of Outcome Measures**

**Primary Outcome Measure:** ≥ 50% pain relief

**Secondary Outcome(s):** Improvement of function, reduction in the amount of oral medication, decrease in side effects from systemic drugs, and improvement in quality of life (QOL).

Pain and symptom improvement is evaluated on both short-term (12 months or less) and long-term (more than 12 months) basis.

**Review Methods**

**Review Criteria**

Each study was evaluated by 2 physicians for the stated criteria and any disagreements were resolved by a third physician.

If there was a conflict of interest with the reviewed manuscripts with authorship or any other type of conflict, the involved authors did not review the manuscripts for quality assessment, clinical relevance, evidence synthesis, or grading of evidence.

**Methodological Quality Assessment**

The quality of each individual article used in this analysis was assessed by modified Cochrane review criteria with weighted scores (59) for randomized trials and the Agency for Healthcare Research and Quality (AHRQ) quality criteria for assessment of observational studies (60) with consensus-based weighted scoring developed by the guidelines committee of the American Society of Interventional Pain Physicians (ASIPP) which has been utilized in several other evaluations (28,36,38,48,61-68).

Only the studies scoring at least 50 of 100 on weighted scoring criteria were utilized for analysis.

**Data Extraction**

A standardized form was used to extract the relevant data on the methods used, participants, interventions, outcome measures used and timing of outcome measurement, reported side effects, and the main results.

**Analysis of Evidence:**

Qualitative analysis was conducted using 5 levels of evidence as described by AHRQ, ranging from Level I to Level III with 3 subcategories in Level II, as illustrated in Table 1 (69).
Recommendations

Grading recommendations were based on Guyatt et al’s criteria as illustrated in Table 2 (70).

Results

Figure 1 illustrates the results of the literature search for intrathecal infusion systems.
Intrethecal Infusion Systems for Chronic Non-Cancer Pain

Fig. 1. The flow diagram illustrating published literature evaluating intrathecal infusion systems.
After a comprehensive search and evaluation of the available studies for intrathecal infusion devices as well as drugs infused for non-cancer pain, qualified studies were tabulated. Overall, 15 of the intrathecal infusion for non-cancer pain were identified (52-57,71-79).

Methodologic Quality Assessment
Nine studies (52,54,56,57,71-75) met inclusion criteria for methodologic quality assessment with at least 12 months of follow-up. However, there were no randomized trials. Of the 9 studies, 4 studies were excluded because they included less than 25 patients. Of the studies not meeting inclusion criteria, one study included 23 patients (55), the second study included 16 patients (53), the third study was excluded for sample size of 24 (75), and another study included 16 patients (77).

Table 3 illustrates the methodologic quality assessment of 5 observational studies (54,71-74) evaluating non-cancer pain. The quality assessment scores of the included studies (54,71-74) ranged from 49 to 60 with only 4 (71-74) meeting inclusion criteria for evidence synthesis (score ≥ 50).

Study Characteristics
Table 4 illustrates the descriptive characteristics of the intrathecal infusion device studies evaluating non-cancer pain included in methodologic quality assessment.

In 1996, Winkelmüller & Winkelmüller (71) evaluated the long-term effects of continuous intrathecal opioid treatment for chronic pain of nonmalignant etiology. Patients had neuropathic as well as nociceptive and mixed types of pain (majority of the patients – 73 of 120, had pain arising from lumbar spinal surgeries). The follow-up period was from 6 months to 5.7 years, with only 36 patients followed up for > 4 years. The deafferentation pain and neuropathic pain showed the best results on a long-term basis with 62% to 68% reduction in pain. Thirty-one or 25.8% of the 120 cases were considered treatment failures. Throughout the follow-up period, 74.2% of the patients benefited from the intrathecal opioid therapy, with an average pain reduction after 6 months of 67.4% and, as of the last follow-up examination, it was 58.1%. Ninety-two percent of the patients were satisfied with the therapy and 81% reported an improvement in their QOL.

Although the authors describe a lengthy follow-up period ranging from 6 months to 5.7 years, it is not clear how many patients had been followed up for more than 12 months. The last follow-up period is mentioned in several of the parameters but is not clearly defined. Based on the review of the data, it appears that 36 patients received intrathecal opioid medications for a period of more than 4 years. Further, there were multiple complications with undesirable incidents and failures. They removed 25 pumps for various reasons. Twenty-six percent of the cases were considered as treatment failures. The overall success rate in 89 of the 120 patients benefiting from continuous opioid therapy over an observation period of 0.5 to 5.7 years is highly variable.

Roberts et al (72) collected data for intrathecal opioid administration in chronic non-cancer pain in 88 patients, out of which 67 had returned the questionnaires. The majority of the patients had failed lumbar spine surgery syndrome (63%). Other indications for the implantable drug administration systems (DASs) included lumbar spine pain and radicular symptoms without surgery, cervical failed spine surgery, complex regional pain syndrome (CRPS), pancreatitis, and others. The authors focused on global pain relief, physical activity, work status, side effects, patients who ceased the therapy, and patient satisfaction. Although the observed patient satisfaction was high and the level of activity had increased, the return to work status did not change in the majority of the patients. The mean morphine does at 6-month follow-up was 9.95 mg/day, which increased to 15.26 mg/day at 36-month follow-up, a relatively high dose. The patients had a long history of chronic pain with a mean duration of 9.8 years. Most patients had been receiving opioids and had been treated with various other modalities. The majority of the patients (82%) reported pain relief greater than 50% and an increase in their activity levels. There was also a significant reduction in their oral medication intake, which would be expected given the high doses of intrathecal infusions. Reported side effects were excessive sweating, weight gain, difficulty with concentrating or memory, nausea/vomiting, arthralgia, peripheral edema, pruritus, sexual dysfunction, reduced libido, and menstrual abnormalities. Their reported difficulties with the system were high, and 40% of the patients required at least one surgical procedure to correct a technical problem. The authors concluded that there was improvement in analgesia with a reduction in medication intake, but it was offset by significantly increased intrathecal dosage. Also, the 40% device/catheter revision rate may not be ac-
### Table 3. Methodologic quality assessment of observational studies evaluating non-cancer pain.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Question</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>• Clearly focused and appropriate question</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Study Population</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>• Description of study population</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>• Sample size justification</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3. Comparability of Subjects</td>
<td>22</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>• Specific inclusion/exclusion criteria for all groups</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>• Criteria applied equally to all groups</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>• Comparability of groups at baseline with regard to disease status and prognostic factors</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>• Study groups comparable to non-participants with regard to confounding factors</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>• Use of concurrent controls</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Comparability of follow-up among groups at each assessment</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
</tr>
<tr>
<td>4. Exposure or Intervention</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>• Clear definition of exposure</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>• Measurement method standard, valid and reliable</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>• Exposure measured equally in all study groups</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5. Outcome measures</td>
<td>20</td>
<td>14</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>• Primary/secondary outcomes clearly defined</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>• Outcomes assessed blind to exposure or intervention</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Method of outcome assessment standard, valid and reliable</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>• Length of follow-up adequate for question</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6. Statistical Analysis</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>• Statistical tests appropriate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>• Multiple comparisons taken into consideration</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Modeling and multivariate techniques appropriate</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Power calculation provided</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Assessment of confounding</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Dose-response assessment if appropriate</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7. Results</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>• Measure of effect for outcomes and appropriate measure of precision</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>• Adequacy of follow-up for each study group</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>8. Discussion</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>• Conclusions supported by results with possible biases and limitations taken into consideration</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>9. Funding or Sponsorship</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>• Type and sources of support for study</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>100</td>
<td>53</td>
<td>49</td>
<td>50</td>
<td>53</td>
<td>60</td>
</tr>
</tbody>
</table>

Adapted and modified from West S et al. Systems to Rate the Strength of Scientific Evidence, Evidence Report, Technology Assessment No. 47. AHRQ Publication No. 02-E016 (60).
Table 4. Descriptive characteristics of the intrathecal infusion device studies evaluating non-cancer pain, meeting methodologic assessment criteria.

<table>
<thead>
<tr>
<th>Study/Methods</th>
<th>Participants</th>
<th>Intervention(s)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
<th>Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winkelmüller &amp; Winkelmüller 1996 (71)</td>
<td>120 patients with non-cancer pain followed from 6 mos. to 5.7 yrs. Patients had nociceptive–neuropathic pain due to multiple lumbo-scapal operations.</td>
<td>Intrathecal morphine (+ buprenorphine, Clonidine, fentanyl, or NaCl in various combinations) via implantable pump. Additional medications were included as a combination and consisted of bupivacaine, Clonidine, fentanyl, and buprenorphine.</td>
<td>Outcome measurement with VAS and McGill pain questionnaire, level of activity, mood, QOL, complications and side effects.</td>
<td>Deafferentation pain and neuropathic pain showed the best long-term results, with 68% and 62% pain reduction. Pain reduction after 6 months was 67.4% and, as of the last follow-up examination, it was 58.1%. 92% patients were satisfied with the therapy and 81% reported an improvement in their QOL. VAS measured pre-implant = 93.6, 6 mo. Later VAS = 30.5, Last f/u VAS = 39.2. Best initial reduction in pain (77%) in nociceptive group. Which decreased to 48% at last f/u improved level of activity; 67% pts. satisfied with pain level, 81% improved QOL. Morphine was the most effective and tolerated substance. Complications: 14 pumps replaced, 25 pumps removed (28.5% pts considered failures).</td>
<td>Long-term administration of spinal opioid medications for nonmalignant pain is encouraging in carefully selected patients. Good results were achieved in a total of 74.2% of the patients, and a pain reduction of approximately 60% was reported even after long-term opioid application.</td>
</tr>
<tr>
<td>Roberts et al 2001 (72)</td>
<td>88 patients with implanted drug adm. systems (1989 – 1996). Diagnoses included failed spinal surgery (n = 55), lumbar spinal or radicular pain without surgery (n = 6), CRPS I (5), cervical failed spinal surgery (n = 4), crush fractures (n = 3), chronic pancreatitis (n = 3), others (n = 12).</td>
<td>Intrathecal opioids (morphine) via implantable drug administration systems after a successful trial.</td>
<td>Global pain relief, physical activity levels, medication consumption, work status, intrathecal opioid side-effects, proportion of patients who ceased therapy, and patient satisfaction.</td>
<td>Mean pain relief – 60% with 74% of patients (36 of 49) reporting increased activity levels. Significant reduction in oral medications. Frequent side effects such as sexual dysfunction, menstrual disturbance were reported. 88% patients reported high satisfaction levels. Change in work status was not seen in the patients.</td>
<td>Intrathecal opioid therapy appears to have a place in the management of chronic non-cancer pain. Therapy does not seem to be significantly inhibited by the development of tolerance.</td>
</tr>
<tr>
<td>Deer et al 2002 (73)</td>
<td>109 consecutive patients for bupivacaine + opioid compared with opioid alone. 84 non-cancer patients and 25 cancer patients.</td>
<td>Implantable drug infusion systems delivering opioid alone vs opioid + bupivacaine.</td>
<td>Primary outcome measure – pain relief via VAS score, secondary outcomes amount of medications via other routes (oral/transdermal), ER visits, routine office visits, patient satisfaction. Neurological complications reviewed with combined drugs.</td>
<td>With combination (bupivacaine + opioid) infusion the pain relief was significantly better, the number of oral opioids used were significantly less, number of oral nonopioid adjuvants were reduced, number of doctor’s visits were less in the combined arm, number of pain clinic visits were less, the number of emergency visits were significantly less and patient satisfaction was better. Total dose of morphine was reduced by 23% with combined drugs.</td>
<td>Bupivacaine, when used in combination with opioids, is a helpful and safe method of treatment in a select population of patients who have not responded to intrathecal opioids alone.</td>
</tr>
<tr>
<td>Thimineur et al 2004 (74)</td>
<td>69 patients divided into 2 groups. 38 pts. received intrathecal pump, 31 did not (patients with unsuccessful trial or declined intrathecal therapy). Another group of new patients (n = 41) used as comparative group.</td>
<td>Intrathecal morphine, hydromorphone, fentanyl, Clonidine, Bclonfen, bupivacaine, and methadone. Non intrathecal group continued the pre-study medications (systemic opioids).</td>
<td>Multiple questionnaires – symptom checklist 90-R, SF36 Health study, Beck depression questionnaire, McGill pain questionnaire – short, Oswestry disability index, Pain drawing. VAS (1–10). Evaluations done at base line and then every 6 months for 3 years.</td>
<td>Intrathecal treatment had a significant impact on pain, function, and mood among study patients. Non-recipients deteriorated despite escalation of oral opioids and provision of injection treatments. The base line opioid requirements were higher in the pump recipients (PR) than non-recipients (NR). At 36 months, the average daily oral morphine dose had significantly decreased for PR group and increased for NR.</td>
<td>Intrathecal opioid therapy for non-cancer pain should be considered appropriate only when all other conservative medi cal management has been exhausted.</td>
</tr>
</tbody>
</table>
Intrethecal Infusion Systems for Chronic Non-Cancer Pain

ceptable. Despite a significantly higher intrathecal dose, the authors claim that dose escalation did not appear to be a problem.

Deer et al (73) compared the effectiveness of a combination of bupivacaine with opioids and opioid alone. Their patient population included non-cancer as well as cancer pain (with spinal metastases), however the majority of patients had non-cancer pain (back and leg pain after unsuccessful back surgery). Patients served as their own comparison arm as they were on opioid alone prior to the inclusion of bupivacaine. Inclusion criteria were VAS more than 6 on at least 3 consecutive visits while on opioid alone. Consuming opioids via multiple routes was not an exclusion criterion. Patients with neurological complications while on opioid alone were excluded. Outcome data included pain levels, ER visits, patient satisfaction, regular clinic visits as well as medication intake via other routes. Mean exposure to bupivacaine was 62.2 ± 21.3 weeks for all patients, but the cancer patients' data obtained for a mean of only 28 weeks may have skewed this number. All but one patient experienced some reduction in pain as well as need for opioids via other routes. Use of non-opioid medications was also reduced but was statistically insignificant. No significant neurological sequelae from the use of bupivacaine were noted in the majority of patients. The authors concluded that in patients treated with intrathecal opioids, the addition of bupivacaine may improve outcomes. Side effects were rare and there was no evidence of neurological sequelae from the addition of bupivacaine to opioids via intrathecal infusion devices.

Thimineur et al (74) evaluated the long-term outcome of intrathecal opioid therapy in chronic non-cancer pain prospectively and included 2 comparative groups to improve the understanding of the selection criteria and relative severity of intrathecal pump recipients. Data analysis suggests the study group of pump participants had improvements in pain, mood, and function from baseline to 36 months. However, the average reductions in pain in this study were less impressive than several previous investigations. The authors have not described the proportion of patients with significant pain relief of 50% or more. They concluded that intrathecal opioid therapy for non-cancer pain should be considered appropriate only when all other conservative medical management has been exhausted. Further confounding factors in this study included opioid medication administered to the recipients, along with injection treatments.

Of the studies not meeting inclusion criteria, Shaladi et al (75), in 2007, studied a group of older patients with severe osteoporosis and recent vertebral fracture. A clearly focused study evaluated the QOL in these patients with intrathecal morphine using a specific evaluation questionnaire for such populations with the Questionnaire of the European Foundation of Osteoporosis (QUALEFFO) on which a maximum score of 150 indicates poor health. This questionnaire evaluates QOL, domestic work, ambulation, and perception of health status, and was given to the patients after the implant as well as at one-year follow-up. Patients were of an average age of 74.3 years and had a trial of conservative treatment for at least one-month with oral or transdermal opioids and still had a VAS of ≥ 7. Also considered for implant were patients with severe side effects with systemic opioids such as vomiting, itching, constipation, or urinary retention, all resistant to pharmacologic therapy. There is mention of “drug addiction” as one of the inclusion criteria. Patients had ≥ 50% improvement in pain after a trial of intrathecal morphine prior to the pump implant. Mean morphine dose, at trial, was 0.47 mg/h, which corresponded to a mean VAS value of 3.7. The mean morphine dose used at pump implant was 0.33 mg/h and the mean morphine dose after one-year from the pump implantation was 0.68 mg/h. The mean functional score QUALEFFO before trial was 114.7. After pump implant the mean QUALEFFO score had fallen to 92.1, and, after one-year, the mean QUALEFFO score fell to 79.1. Considering the pain from a recent vertebral fracture may normally improve after 6 months to a year, the contribution of the pump implant to the reduction in pain scores in this study is unclear. A comparative group of patients without intrathecal morphine would have clarified some questions as to the natural outcome of this pain type as well as the functional improvement of patients without any intrathecal morphine. With promising data on vertebroplasty as well as kyphoplasty, which are relatively cheaper options compared to an intrathecal infusion pump, and are also a one time treatment option, intrathecal morphine for vertebral fractures may have limited applications to patients who are not candidates for vertebral augmentation procedures. Other questions that remain unanswered are the long-term effects as well as side effects of such a high does of morphine (16.32 mg per day) after 2 years or more.
Effectiveness
Table 5 illustrates results of the effectiveness of intrathecal infusion systems.

Of the 4 observational studies (71-74) meeting quality assessment criteria evaluating intrathecal infusion systems, 2 studies (71,72) showed positive results for short- and long-term relief. The results were not available for one study (73) and were negative for one study (74).

Level of Evidence
The evidence for intrathecal infusion systems is either Level II-3 or Level III (limited) based on U.S. Preventive Services Task Force (USPSTF) criteria.

Recommendation
Based on Guyatt et al’s criteria (70), the recommendation for intrathecal infusion systems is 1C/strong recommendation based on the current evidence derived from observational studies and the recommendation may change based on future evidence.

Discussion
The present systematic review with 5 observational studies meeting methodologic quality assessment (71-75) indicates that the evidence is Level II-3 or III (limited) based on USPSTF criteria with a recommendation of 1C/strong based on the evidence derived from observational studies. The evidence illustrated in this systematic review is similar to the previous systematic reviews, which also suffered from a paucity of evidence. It is rather surprising that despite multiple years of usage, numerous implants across the world, and significant arguments in favor of effectiveness, the available literature is so sparse.

This review focused on the use of intrathecal devices for intrathecal infusions of single as well a combination of drugs for chronic non-cancer pain only. Keeping the inclusion criteria stricter than some of the previous reviews helped filter the best evidence published to date for this modality. The definition of long-term relief as relief for longer than one year also provides robust criteria in the present systematic review.

Intrathecal infusion devices for chronic non-cancer pain have been utilized for the last quarter century. Although there was more focus on cancer pain earlier on, in the mid-nineties chronic non-cancer pain was also thought to be a major indication for intrathecal infusion of opioid medications. More combinations and substitutions were gradually introduced into practice over the course of several years. Although initial responses to this modality were very promising, drug tolerance as well as side effects gradually came into the picture and more and more complications began to be published. Cancer patients, having a more limited life span, did not provide the data on long-term chronic use of this modality.

Table 5. Results of published studies of effectiveness of intrathecal infusion systems.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Participants</th>
<th>Pain Relief</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12 mos.</td>
<td>12 mos.</td>
</tr>
<tr>
<td>Winkelmüller &amp; Winkelmüller 1996 (71)</td>
<td>O 53 120</td>
<td>74% 74%</td>
<td>P P</td>
</tr>
<tr>
<td>Roberts et al 2001 (72)</td>
<td>O 50 88</td>
<td>82% 82%</td>
<td>P P</td>
</tr>
<tr>
<td>Deer et al 2002 (73)</td>
<td>O 53 109</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>Thimineur et al 2004 (74)</td>
<td>O 60 38 - pump, 31 - non-pump</td>
<td>NA NA</td>
<td>N N</td>
</tr>
<tr>
<td>Shaladi et al 2007 (75)</td>
<td>O 55 24</td>
<td>100% 100%</td>
<td>P P</td>
</tr>
</tbody>
</table>

O = observational; P = positive; N = negative; NA = not applicable
A significant proportion of side effects and complications have been reported (80,81). A 21.6% complication rate was shown in a retrospective analysis of 419 patients with at least 6 months of infusion time (81). In a small group of cancer patients the complication rate for infection, catheter failure, or pump failure was very limited (82). Technical complications include subdural intrathecal catheter placement (83), dural puncture and subdural injection (84), tension pseudomeningocele associated with retained intrathecal catheter (85), intrathecal granuloma formation (86-88), peripheral edema (89,90), and multiple treatment challenges and complications with ziconotide monotherapy in established pump patients (91). Further side effects include hormonal changes and respiratory depression. Several studies have reviewed intrathecal infusion devices in various forms. Most of them focused on a variety of indications (such as spasticity as well as cancer pain). The efficacy of intrathecal infusions may be better studied for separate indications as the follow-up times as well as the drugs contained in the infusion may have a significant impact on the outcomes of the study as well as the overall recommendations for this modality (92-94).

More recently, a focused review was published by Smith et al (95). The authors found that the evidence for implantable intrathecal infusion systems was strong for short-term improvement in pain of malignancy or neuropathic pain. The evidence was moderate for long-term management of persistent pain. Reasonably strong evidence exists for the use of long-term intrathecal analgesic therapy in the alleviation of cancer pain; however, the evidence supporting long-term efficacy in persistent non-cancer pain is less convincing. They concluded that the current body of literature supports the use of intrathecal agents for the treatment of moderate or severe pain related to cancer and non-cancer origins. However, the lack of systematic reviews of the published literature does not allow for proper grading of the quality of these studies. Combining various indications for this modality also prevents one from standardizing the recommendations.

One of the few prospective trials was published by Thimineur et al (74) in 2004. Two groups of patients were studied either with intrathecal infusion systems or without intrathecal infusion. Patients had chronic non-cancer pain. They also included a third group in the study for comparison. This group consisted of patients who were new recruits to the pain clinic. In this 3 year study, they evaluated several parameters at 6 month intervals. These parameters included Symptom Checklist-90 (SCL-90), SF-36 Health Survey (SF-36), Beck Depression Inventory, McGill Pain Questionnaire (short form) (SF-MPQ), Oswestry Disability Index (ODI), pain drawings, and pain rating on the visual analog scale (VAS). Their results indicated that the group that received intrathecal therapy had better pain control, mood, and function from the baseline data. The non-recipients had significant worsening of their pain and function. However, even with the improved pain, mood, and function, the intrathecal group was still worse off than the new patient group at 36 months. This may be because of the long standing history of pain and dysfunction in the group that did receive intrathecal therapy. Interestingly, even the intrathecal group continued a high amount of opioids through other routes. Another fact is that the intrathecal infusions were not limited to opioids alone, which may have contributed to this apparent success.

Overall, the studies have shown a good long-term benefit from intrathecal infusion devices used for chronic non-cancer pain. Although the life span of patients should be considered several decades after pump implants, the studies seem to show a stable rate of analgesia at least for less than 10 years. This effect may not be as pronounced once the period is extended to more than a decade. Also, the formation of inflammatory masses in the form of granulomas is a major deterrent with this modality. As previously thought, the granuloma formation does not depend on the drug itself and has been seen with morphine as well as baclofen infusions. A Canadian study demonstrated the cost effectiveness of intrathecal infusion devices. Kumar et al (55) looked at the cost of implanting a programmable drug delivery pump vs. conservative treatment of chronic pain. Their patient population consisted of failed back syndrome. Successful outcomes were measured using the pain scale, ODI, and QOL. The cumulative costs for intrathecal drug delivery during a 5-year period were $29,410, as opposed to $38,000 for conservative treatments. High initial costs of equipment required for intrathecal drug delivery were recovered by 28 months. After this time, managing patients with conservative treatments became more expensive for the remainder of the follow-up period. The ODI showed a 27% improvement for patients in the intrathecal drug delivery group, compared with a 12% improvement in the control group. This is an important finding and may help justify the

www.painphysicianjournal.com
initial cost of the implantable pump system. However, considering the life of the programmable pump, there is obviously a high added cost for maintaining this treatment option beyond the initial life of the pump for the patient’s life span.

The limitations of this systematic review includes the paucity of literature. There were no randomized trials available meeting the inclusion criteria. Further, observational studies are also very few. Systematic reviews in interventional pain management are signs of progress in the effort to keep pace with advances in health care innovations. Systematic reviews have been growing at a rapid pace in interventional pain management (96,97). Systematic reviews are at the core of evidence-based medicine which is a shift in medical paradigms that acknowledges that intuition, unsystematic clinical experience, and pathophysiologic rationale are insufficient grounds for clinical decision-making (98-100). In the hierarchy of strength of evidence for treatment decisions, N of 1 RCT occupies the top place, followed by systematic reviews of randomized trials, systematic reviews of observational studies, followed by unsystematic clinical observations. Thus, observational studies and their systematic reviews are lower in the hierarchy than the randomized trials and their systematic reviews. Randomized trials provide valuable evidence about treatments and other interventions. However, most of the research in clinical practice comes from observational studies (101-103). Randomized trials work by first assuming there is no difference between a new and an old or placebo treatment to prove the null hypothesis (104). In simplistic terms, standard RCTs are designed to show that treatments do not work, rather than to demonstrate that treatments do work. Numerous criticisms, politics, and a lack of understanding of randomized trials have resulted in allegations that the research performed to test new treatments has often been of poor quality. Thus, clinicians have criticized the research establishment for failing to provide answers to relevant clinical problems of everyday practice (105,106). Most questions in medical research are investigated by observational studies (1,28,31,32,36-42,107-115) which are more likely to provide an indication of daily medical practices (116). Thus, proponents of observational studies believe that observational studies are just as effective as RCTs. However, from a methodologic perspective, the 2 types of studies are considered complementary rather than opposing (109). Thus, observational studies and RCTs can be viewed as expressions in the setting of modern clinical research of the steps of observation and experimentation that form the basis of scientific methodology. The observational step is used to uncover patterns and formulate hypothesis regarding cause-and-effect relationships, which is followed by the experimentation step in which the hypotheses formed in the observational setting are confirmed or refuted in an experiment in which the independent variables are controlled by the experimenter (109,117,118). A major drawback of observational research is of poor reporting as it results in an inability to assess the strengths and weaknesses of the investigations (102,103,117,118). These deficiencies can be overcome by an assessment of the methodologic quality of observational studies. There are several instruments for methodologic quality assessment of randomized trials (100). In this systematic review, we have utilized West et al’s (60) described criteria from the AHRQ evidence report of technology assessment. They assessed 19 systems relating to observational studies or investigations prior to developing the criteria. Consequently, we believe that this systematic review provides appropriate information.

The major argument made by researchers is that interventions such as intrathecal implantables may not be performed in a double blind manner. However, they can be performed as equivalence or non-inferiority trials with randomization, but without blinding. In fact, multiple studies describing interventions have been performed in this manner (27-38,61-68,119-123).

**Conclusion**

Intrathecal infusion devices used for the treatment of chronic intractable pain provide positive long-term outcomes and may have a role as an advanced-stage therapy for refractory pain.

This systematic review illustrates Level II-3 or Level III (limited) evidence for intrathecal infusion systems for long-term relief in chronic non-cancer pain.

**Acknowledgments**

The authors wish to thank the editorial board of *Pain Physician*, for review and criticism in improving the manuscript; Vidyasagar Pampati, MSc, statistician; Sekar Edem for assistance in search of literature; and Tonie M. Hatton and Diane E. Neihoff, transcriptionists (Pain Management Center of Paducah), for their assistance in the preparation of this manuscript.
References


43. Specialty Utilization data files from CMS: www.cms.hhs.gov


Intrathecal Infusion Systems for Chronic Non-Cancer Pain


