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Systematic Review

# Intrathecal Therapy for Cancer and Non-Cancer Pain

Salim M. Hayek, MD, PhD[1], Timothy R. Deer, MD[2], Jason E. Pope, MD[3], Sunil J. Panchal, MD[4], and Vikram Patel, MD[5]

From: [1]University Hospitals and Outcomes Research Consortium, Cleveland, OH; [2]Center for Pain Relief, Charleston, WV; [3]Napa Pain Institute, Napa, CA; [4]National Institute of Pain, Tampa, FL; and [5]ACMI Pain Care, Algonquin, IL.

Dr. Hayek is Associate Professor, Department of Anesthesiology, Chief of the Division of Pain Medicine, University Hospitals of Cleveland, Cleveland, OH; and a member of the Outcomes Research Consortium, Cleveland, OH. Dr. Deer is Medical Director, The Center for Pain Relief, and Clinical Professor, Anesthesiology, West Virginia University School of Medicine, Charleston, WV. Dr. Pope is partner, Napa Pain Institute, Napa, CA. Dr. Panchal is President of the National Institute of Pain, Tampa, FL. Dr. Patel is Medical Director of ACMI Pain Care, Algonquin, IL.

Address Correspondence:
Salim M. Hayek, MD, PhD
Division of Pain Medicine
University Hospitals
11100 Euclid Ave
Cleveland, OH 44106
Email: salim.hayek@UHhospitals.org

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**Background:** Intrathecal drug infusion therapy is usually considered when spinal-acting analgesics or antispasmodics administered via the oral or transdermal routes fail to control patients' pain or are associated with unacceptable side effects. The intrathecal administration of centrally acting agents bypasses the blood-brain-barrier resulting in much higher cerebrospinal fluid (CSF) concentrations while using reduced amounts of medication to achieve equipotent doses. The intrathecal approach is associated with higher rates of satisfactory pain relief and lower rates of treatment failures and technical complications compared to the epidural route. A paucity of randomized controlled trials (RCTs) has led to concern regarding proper use, selection criteria, and safety of these devices. Cost effectiveness and comparative therapies have now also become a focus of discussion.

**Objective:** The purpose of this systematic review is to evaluate and update the available evidence for the efficacy and safety of intrathecal infusions used in long-term management (> 6 months) of chronic pain. This paper will not focus on intrathecal administration for spasticity or movement disorders.

**Study Design:** A systematic review of intrathecal infusion through implanted drug delivery devices for chronic pain.

**Methods:** Literature search through EMBASE, Medline, Cochrane databases, and systematic reviews as well as peer-reviewed non-indexed journals from 1980 to December 2010. Studies are 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 for chronic non-cancer is pain relief (short-term relief ≤ one-year and long-term > one-year), whereas it is 3 months for cancer. Secondary outcome measures of improvement in functional status, psychological status, return to work, and reduction in opioid intake.

**Results:** The level of evidence for this systematic review of non-cancer pain studies meeting the inclusion criteria of continuous use of an intrathecal drug delivery system (IDDS) for at least 12 months duration with at least 25 patients in the cohort, is Level II-3 based on USPSTF criteria. The level of evidence for this systemic review for cancer-related pain studies meeting the inclusion criteria of continuous use of IDDS for at least 3 months duration with at least 25 patients in the cohort is Level II-2 based on USPSTF criteria.

**Conclusion:** Based on the available evidence, the recommendation for intrathecal infusion systems for cancer-related pain is moderate recommendation based on the high quality of evidence and the recommendation is limited to moderate based on the moderate quality of evidence from non-randomized studies for non-cancer related pain.

**Key words:** Intrathecal infusion, intrathecal drug delivery device, intrathecal drug delivery system, intraspinal infusion, programmable infusion systems, spinal infusion, intra-spinal infusion devices, baclofen infusion, intrathecal opioids

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Clinical administration of intrathecal opioids for chronic pain shortly followed detection of mu opioid receptors on the dorsal horn of the spinal cord (1,2). The Food and Drug Administration (FDA) approval of Medtronic's intrathecal drug delivery system (IDDS) in 1991 led to a progressive increase in the use of intrathecal analgesics for the relief of chronic pain, both cancer and non-cancer related (3). Inadequate pain relief with conservative medical therapy and/or intolerable side effects to oral/transdermal opioids or failure of interventional and surgical techniques are the main reasons for considering the intrathecal route of drug administration (4-7).

Chronic pain is a major burden and an expensive health problem in industrialized countries (5,8). Chronic pain can be cancer related and non-cancer related with the latter accounting for the vast majority of patients. Pain of spinal origin, and in particular chronic low back pain, is foremost in prevalence and significance among chronic non-cancer pain (9,10). Surgical rates for back pain have increased dramatically in the US over the past 3 decades, in particular for spinal fusion surgeries despite limited reports of efficacy (11). Failed Back Surgery Syndrome (FBSS) or lumbar post-laminectomy syndrome has become a common modern disorder whereby patients suffer with chronic back and/or leg pain following lumbar spinal surgery. FBSS is the most common indication for IDDS placement (12).

Implanted intrathecal infusion systems bypass the blood brain barrier delivering medications directly into the intrathecal space. Currently, only 2 agents are FDA approved for intrathecal use for pain, namely preservative-free morphine and ziconotide (13,14). However, a number of other agents including bupivacaine, clonidine, and fentanyl are commonly used (15). Consensus guidelines regarding intrathecal drug delivery have been published since 2000 (16) with subsequent updates and revisions (17-19). IDDS have become widely used over the past 2 decades to treat pain of neuropathic, nociceptive, and mixed physiological origin in both cancer and non-cancer disease states. This therapy has been reserved as a late stage treatment for those who have responded to oral or transdermal medications, but were not good candidates for the continuation of that therapy because of side effects or lack of persistent efficacy. The use of these therapies can be life changing and can result in significant pain relief, improved quality of life, and reduced side effects, but these accolades do not come without expense or risks (5,6,20-28). However, despite its touted benefits, questions regarding its efficacy and utility remain.

Multiple systematic reviews and health technology assessments have been published without conclusive evidence leading to continued debate of the clinical effectiveness, cost effectiveness, and safety (5,6,24,29,30). In the recent systematic review by Patel et al (24) only 5 observational studies met inclusion criteria, yielding limited evidence. This systematic review of randomized and non-randomized studies for cancer and non-cancer pain is undertaken to assess the benefits, risks, and efficacy of IDDS based on the currently available literature.

## Methods

### Search Strategy

Bibliographic resources such as PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Controlled Trials Register, were used to search for English language studies published from 1966 until October 30, 2010 (the date of the last search). To identify the studies the following criteria were used: a) study design: all designs (prospective, retrospective, technical reports, randomized clinical trials); b) study subjects: subjects with chronic pain including cancer pain patients and non-cancer pain patients with or without history of previous spine surgery; c) types of interventions: IDDS implanted and followed for at least 3 months for cancer pain and 12 months for non-cancer pain; d) keywords used to search were intrathecal pump for pain, intrathecal infusion, spinal infusion, morphine pump, intrathecal drug delivery system, spinal pump, intrathecal therapy. Excluded were case reports, technical reports, surveys, animal studies, and in-vitro pump evaluations.

The search was performed by 2 reviewers, in an unblinded standardized manner, and any discrepancies were evaluated by a third reviewer and consensus was reached.

### Study Selection

Search results from all databases were combined and duplicates were removed. Reference lists from retrieved articles were also reviewed for additional relevant studies that were not identified in our search. All articles were triaged for inclusion by the authors for suitability prior to review. Studies were selected for inclusion if the methods clearly indicated that an IDDS was used for management of chronic pain. The

relevant data on the methodology and outcome measures were collected. The following criteria were used for inclusion in this review: two unblinded reviewers, using standard practice, carried out the study selection; a third reviewer evaluated any discrepancies and all 3 reached a consensus.

## Inclusion 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 chronic pain for long-term use. Studies must have a specific indication for intrathecal infusion and the drug injected. A minimum of 3 months of follow-up was available for studies on cancer pain patients. A minimum of 12 months of follow-up was available for studies on non-cancer pain or studies involving both cancer and non-cancer pain patients. Clear documentation of patient outcomes and complications should have been provided. Number of patients evaluated must have been at least 24.

Inclusion criteria were assessed by 2 unblinded reviewers, in a standardized manner, and a third reviewer evaluated any discrepancies and consensus was reached.

## Exclusion Criteria

Lack of clear documentation of infusion systems or mixed delivery methods. Externalized infusion systems for short-term use. Studies for chronic non-cancer pain with less than 12 months follow-up and studies of cancer related pain with less than 3-month follow-up. Case reports, technical reports, surveys, animal studies, and in-vitro pump evaluations.

Three reviewers were involved: 2 unblinded reviewers, using standard methods, assessed exclusion criteria; the third reviewer became involved if a discrepancy happened and working with the other reviewers, reached a consensus.

## Types of Outcome Measures

### *Primary Outcome Measures*

Significant pain relief defined as a minimum of 2-point drop on an 11-point numerical pain scale or a decrease of baseline pain intensity by 30% (31).

### *Secondary Outcome Measures*

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 a short-term (12 months or less) and long-term (more than 12 months) basis for non-cancer pain studies and for 3-months for cancer pain studies.

Working in a standardized manner, outcome measures were assessed by 2 unblinded reviewers, and any discrepancies were evaluated by a third reviewer and consensus was reached.

## Review Methods

### *Methodological Quality Assessment*

The quality of individual articles was evaluated using criteria from the AHRQ publication (Table 1) for observational studies (32-34) and using Cochrane review criteria for RCTs (Table 2) (35-41) with consensus-based weighted scoring utilized by the guidelines committee of the American Society of Interventional Pain Physicians (ASIPP) and others (24,40-64). Only the studies scoring at least 50 of 100 on weighted scoring criteria were utilized for analysis.

The methodologic quality assessment was performed by 2 reviewers, in an unblinded standardized manner, and any discrepancies were evaluated by a third reviewer and consensus was reached.

### *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. 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.

### *Levels of Evidence*

The levels of evidence in making recommendations for care were adapted from the third USPSTF for the AHRQ criteria. 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 3 (65). The level of evidence as assessed by 2 reviewers, in an unblinded standardized manner, and any discrepancies were evaluated by a third reviewer and consensus was reached.

Table 1. *Modified AHRQ quality assessment criteria for observational studies.*

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

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 (172).

Table 2. Modified and weighted Cochrane methodologic quality assessment criteria as described by Koes et al.

| CRITERION | | Weighted Score |
|---|---|---|
| 1. Study population | | 35 |
| A | Homogeneity | 2 |
| B | Comparability of relevant baseline characteristics | 5 |
| C | Randomization procedure adequate | 4 |
| D | Drop-outs described for each study group separately | 3 |
| E | < 20% loss for follow-up | 2 |
| | < 10% loss for follow-up | 2 |
| F | > 50 subject in the smallest group | 8 |
| | > 100 subjects in the smallest group | 9 |
| 2. Interventions | | 25 |
| G | Interventions included in protocol and described | 10 |
| H | Pragmatic study | 5 |
| I | Co-interventions avoided | 5 |
| J | Placebo-controlled | 5 |
| 3. Effect | | 30 |
| K | Patients blinded | 5 |
| L | Outcome measures relevant | 10 |
| M | Blinded outcome assessments | 10 |
| N | Follow-up period adequate | 5 |
| 4. Data-presentation and analysis | | 10 |
| O | Intention-to-treat analysis | 5 |
| P | Frequencies of most important outcomes presented for each treatment group | 5 |
| TOTAL SCORE | | 100 |

Adapted from Koes BW et al. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. *Pain* 1995; 63:279-288 (35).

*Table 3. Quality of evidence developed by AHRQ.*

| | |
|---|---|
| I: | Evidence obtained from at least one properly randomized controlled trial. |
| II-1: | Evidence obtained from well-designed controlled trials without randomization. |
| II-2: | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. |
| II-3: | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence. |
| III: | Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees. |

Adapted from the Agency for Healthcare Research and Quality, U.S. Preventive Services Task Force (USPSTF) (65).

Table 4. *Quality of evidence criteria.*

| Grade of Recommendation/ Description | Benefit vs Risk and Burdens | Methodological Quality of Supporting Evidence | Implications |
|---|---|---|---|
| 1A/strong recommendation, high-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | RCTs without important limitations or overwhelming evidence from observational studies | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1B/strong recommendation, moderate quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | Strong recommendation, can apply to most patients in most circumstances without reservation |
| 1C/strong recommendation, low-quality or very low-quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Observational studies or case series | Strong recommendation but may change when higher quality evidence becomes available |
| 2A/weak recommendation, high-quality evidence | Benefits closely balanced with risks and burden | RCTs without important limitations or overwhelming evidence from observational studies | Weak recommendation, best action may differ depending on circumstances or patients' or societal values |
| 2B/weak recommendation, moderate-quality evidence | Benefits closely balanced with risks and burden | RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | Weak recommendation, best action may differ depending on circumstances or patients' or societal values |
| 2C/weak recommendation, low-quality or very low-quality evidence | Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced | Observational studies or case series | Very weak recommendations; other alternatives may be equally reasonable |

Adapted from Guyatt G, et al. Grading strength of recommendations and quality of evidence in clinical guidelines. Report from an American College of Chest Physicians task force. *Chest* 2006; 129:174-181 (66).

### *Grading Recommendations*

Qualitative recommendations relative to the quality of evidence for each outcome was judged based on criteria established by Guyatt et al (66) as shown in Table 4. Two reviewers assessed grading recommendations, in an unblinded standardized manner, and a third reviewer evaluated any discrepancies and consensus was reached.

## Results

Figure 1 describes the literature search and review conducted for intrathecal drug delivery systems for non-cancer pain. After comprehensive review and grading based on AHRQ assessment criteria for observational studies, 20 studies were identified that met the specified inclusion and exclusion criteria for intrathecal drug delivery for cancer and non-cancer chronic pain (20-22,67-83). Of these, 15 observational studies involved predominantly non-cancer pain patients (20-22,67-73,75-79) and 5 studies examined only cancer pain patients (74,80-83). Of these, 4 were observational cancer pain studies (74,80-82) and one RCT (83) involving only cancer pain patients were identified.

### Methodological Quality Assessment

There were numerous studies on intrathecal drug delivery for cancer pain that were excluded from this literature analysis because of sample size less than 25 patients, lack of 3-month data, or use of externalized pump system (84-90). The follow-up requirement for this review for cancer pain studies was eased down to 3 months compared to 12 months for non-cancer pain; the 3-month mark is more appropriate given the limited lifespan of many cancer pain patients who are considered for intrathecal therapy. Multiple studies for non-cancer pain were reviewed that narrowly failed to meet the inclusion criteria because of sample size < 25 patients, lack of 12 month follow-up, or the survey nature of the study (91-97).

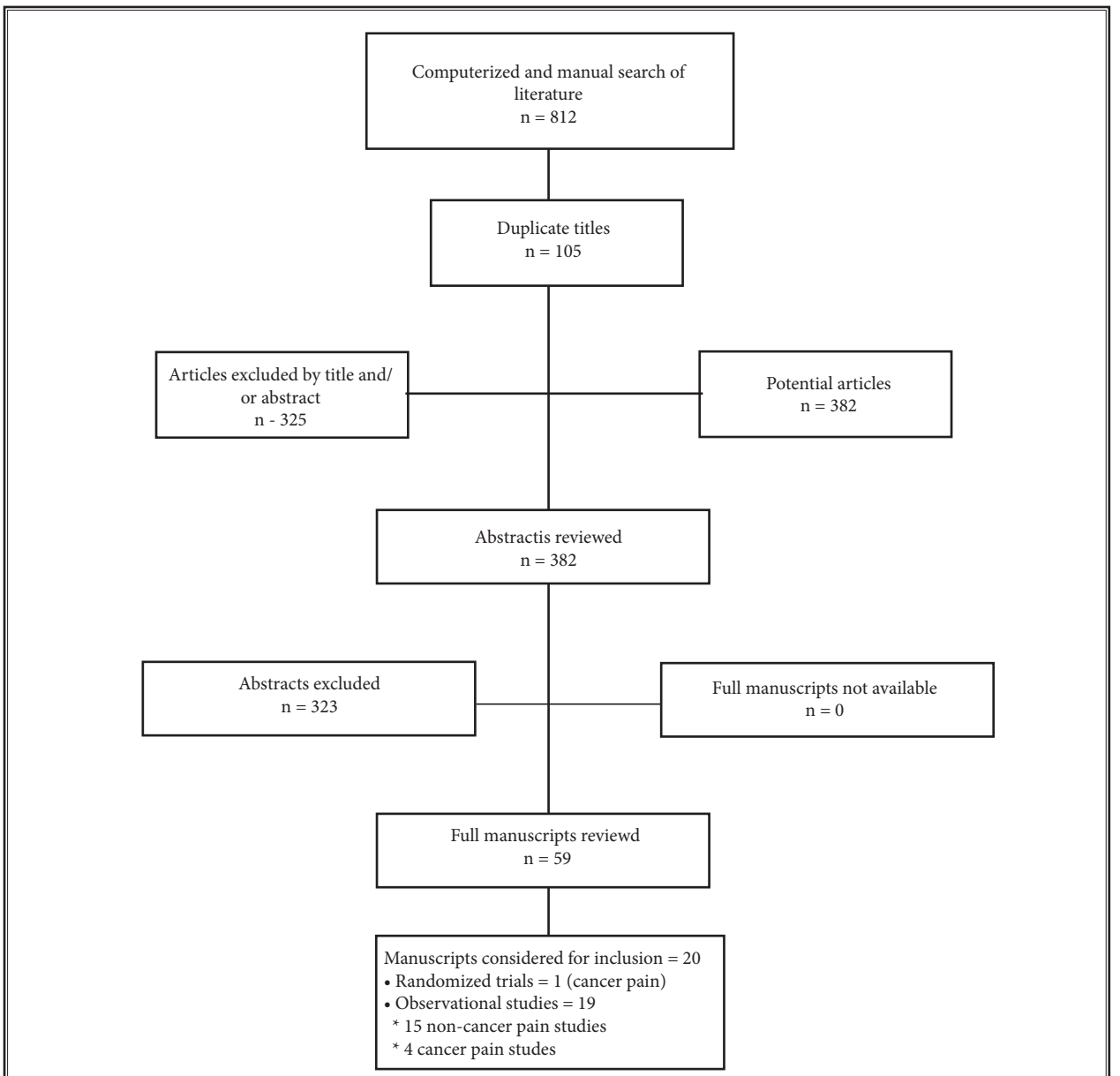


Fig. 1. *The flow diagram illustrating published literature evaluating intrathecal infustion systems.*

Tables 5, 6, and 7 illustrate the methodological quality assessment of studies. Only studies meeting the aforementioned inclusion and exclusion criteria were included; studies with scores < 50 were excluded from analysis.

## Study Characteristics

For cancer related pain, 4 observational studies (74,80-82) and one RCT (83) were identified. Methodological quality scores are displayed in Tables 5 and 6. No RCTs meeting the inclusion criteria were identified

Table 5. *Methodological quality of randomized controlled studies.*

| CRITERION | | Weighted Score | Smith et al, 2002 (83) |
|---|---|---|---|
| Study population | | 35 | 26 |
| A | Homogeneity | 2 | 2 |
| B | Comparability of relevant baseline characteristics | 5 | 5 |
| C | Randomization procedure adequate | 4 | 4 |
| D | Drop-outs described for each study group separately | 3 | 3 |
| E | < 20% loss for follow-up | 2 | 2 |
| | < 10% loss for follow-up | 2 | 2 |
| F | > 50 subject in the smallest group | 8 | 8 |
| | > 100 subjects in the smallest group | 9 | - |
| Interventions | | 25 | 18 |
| G | Interventions included in protocol and described | 10 | 10 |
| H | Pragmatic study | 5 | 5 |
| I | Co-interventions avoided | 5 | 3 |
| J | Placebo-controlled | 5 | - |
| Effect | | 30 | 15 |
| K | Patients blinded | 5 | - |
| L | Outcome measures relevant | 10 | 10 |
| M | Blinded outcome assessments | 10 | - |
| N | Follow-up period adequate | 5 | 5 |
| Data-presentation and analysis | | 10 | 5 |
| O | Intention-to-treat analysis | 5 | - |
| P | Frequencies of most important outcomes presented for each treatment group | 5 | 5 |
| TOTAL SCORE | | 100 | 64 |

for non-cancer pain. Fifteen observational studies in non-cancer related pain were identified that met our criteria and included 8 prospective studies and 7 retrospective studies. These studies involved predominantly non-cancer pain patients; a few studies had a minority of patients with cancer-related pain (21,68,69,72). Table 7 describes scoring of non-cancer pain studies analyzed via the methodological assessment for intrathecal drug delivery in patients with primarily non-cancer chronic pain in reverse chronological order as described in Methods.

Descriptive criteria of eligible cancer and non-cancer pain studies are displayed in Tables 8 and 9, respectively. All studies used pain scores, visual analogue scale (VAS) or numeric rating scale (NRS) as outcome measures. Additional outcome measures included McGill Pain Questionnaires (MPQ) (20,67,70,78,79), medications used (21,22,68,69,73,75,81-83), drug toxicity (83), functional outcomes including Oswestry scores in back pain patients (22,70,78), works status in some non-cancer pain studies (20,22,70,75) as well as other functional parameters specific to the study or condition (21,70,72,76,81-83) or pump parameters (77). All but 3 non-cancer studies examined complications (20,70,77). All studies (cancer and non-cancer related pain) reported positive outcomes. All studies examining pain relief reported improvements in pain scores in patients receiving intrathecal analgesic therapy (20-22,67-70,72-76,78-83).

Study particulars for some of the non-cancer pain studies (69,75,76,78,79) were detailed in the systematic review by Patel et al (24). A recent study by Duse et al

Table 6. *Methodological quality of observational studies for cancer related pain.*

| CRITERION | Weighted Score | Rauck et al, 2003 (74) | Becker et al, 2000 (80) | Onofrio and Yaksh, 1990 (82) | Penn and Paice, 1987 (81) |
|---|---|---|---|---|---|
| 1. Study Question | 2 | 2 | 2 | 2 | 2 |
| • Clearly focused and appropriate question | 2 | 2 | 2 | 2 | 2 |
| 2. Study Population | 8 | 5 | 5 | 5 | 5 |
| • Description of study population | 5 | 5 | 5 | 5 | 5 |
| • Sample size justification | 3 | - | - | - | - |
| 3. Comparability of Subjects for All Observational Studies | 22 | 9 | 9 | 11 | 10 |
| • Specific inclusion/exclusion criteria for all groups | 5 | 4 | 3 | 4 | 3 |
| • Criteria applied equally to all groups | 3 | 1 | 3 | 3 | 3 |
| • Comparability of groups at baseline with regard to disease status and prognostic factors | 3 | 1 | 1 | 3 | 1 |
| • Study groups comparable to non-participants with regard to confounding factors | 3 | - | - | - | - |
| • Use of concurrent controls | 5 | - | - | - | - |
| • Comparability of follow-up among groups at each assessment | 3 | 3 | 2 | 1 | 3 |
| 4. Exposure or Intervention | 11 | 11 | 11 | 7 | 8 |
| • Clear definition of exposure | 5 | 5 | 5 | 3 | 5 |
| • Measurement method standard, valid and reliable | 3 | 3 | 3 | 3 | 3 |
| • Exposure measured equally in all study groups | 3 | 3 | 3 | 1 | - |
| 5. Outcome measures | 20 | 14 | 10 | 13 | 12 |
| • Primary/secondary outcomes clearly defined | 5 | 5 | 2 | 4 | 4 |
| • Outcomes assessed blind to exposure or intervention | 5 | - | - | - | - |
| • Method of outcome assessment standard, valid and reliable | 5 | 4 | 4 | 4 | 3 |
| • Length of follow-up adequate for question | 5 | 5 | 4 | 5 | 5 |
| 6. Statistical Analysis | 19 | 8 | 5 | 12 | 6 |
| • Statistical tests appropriate | 5 | 5 | 2 | 5 | 5 |
| • Multiple comparisons taken into consideration | 3 | 3 | 3 | 3 | - |
| • Modeling and multivariate techniques appropriate | 2 | - | - | 2 | - |
| • Power calculation provided | 2 | - | - | - | - |
| • Assessment of confounding | 5 | - | - | 1 | - |
| • Dose-response assessment if appropriate | 2 | - | - | 1 | 1 |
| 7. Results | 8 | 6 | 7 | 7 | 7 |
| • Measure of effect for outcomes and appropriate measure of precision | 5 | 5 | 4 | 5 | 4 |
| • Adequacy of follow-up for each study group | 3 | 1 | 3 | 2 | 3 |
| 8. Discussion | 5 | 5 | 5 | 5 | 5 |
| • Conclusions supported by results with possible biases and limitations taken into consideration | | 5 | 5 | 5 | 5 |
| 9. Funding or Sponsorship | 5 | - | - | 5 | 5 |
| • Type and sources of support for study | | - | - | 5 | 5 |
| TOTAL SCORE | 100 | 60 | 53 | 67 | 60 |

Table 7. *Methodological quality of observational studies for chronic non-cancer pain.*

| CRITERION | Weighted Score | Atli et al 2010 (68) | Duse et al, 2009 (20) | Ellis et al, 2008 (72) | Ilias et al, 2008 (21) | Shaladi et al, 2007 (76) | Staats et al, 2007 (77) | Doleys et al 2006 (70) | Thimineur et al, 2004 (78) |
|---|---|---|---|---|---|---|---|---|---|
| 1. Study Question | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 |
| • Clearly focused and appropriate question | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 |
| 2. Study Population | 8 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| • Description of study population | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| • Sample size justification | 3 | - | - | - | - | - | - | - | - |
| 3. Comparability of Subjects for All Observational Studies | 22 | 6 | 8 | 13 | 10 | 13 | 9 | 11 | 17 |
| • Specific inclusion/exclusion criteria for all groups | 5 | 1 | 3 | 3 | 3 | 4 | 3 | 4 | 5 |
| • Criteria applied equally to all groups | 3 | 1 | 3 | 1 | 3 | 3 | 3 | 3 | 3 |
| • Comparability of groups at baseline with regard to disease status and prognostic factors | 3 | 1 | 2 | 3 | 1 | 3 | 3 | 1 | 3 |
| • Study groups comparable to non-participants with regard to confounding factors | 3 | - | - | 3 | - | - | - | - | 3 |
| • Use of concurrent controls | 5 | - | - | - | - | - | - | - | - |
| • Comparability of follow-up among groups at each assessment | 3 | 3 | - | 3 | 3 | 3 | - | 3 | 3 |
| 4. Exposure or Intervention | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 6 |
| • Clear definition of exposure | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 3 |
| • Measurement method standard, valid and reliable | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| • Exposure measured equally in all study groups | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | - |
| 5. Outcome measures | 20 | 15 | 15 | 15 | 12 | 15 | 15 | 15 | 13 |
| • Primary/secondary outcomes clearly defined | 5 | 5 | 5 | 5 | 2 | 5 | 5 | 5 | 4 |
| • Outcomes assessed blind to exposure or intervention | 5 | - | - | - | - | - | - | - | - |
| • Method of outcome assessment standard, valid and reliable | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Length of follow-up adequate for question | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 6. Statistical Analysis | 19 | 12 | 8 | 15 | 8 | 10 | 8 | 11 | 4 |
| • Statistical tests appropriate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Multiple comparisons taken into consideration | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | - |
| • Modeling and multivariate techniques appropriate | 2 | 2 | - | 2 | - | 2 | - | - | - |
| • Power calculation provided | 2 | - | - | - | - | - | - | - | - |
| • Assessment of confounding | 5 | - | - | 5 | - | - | - | 3 | - |
| • Dose-response assessment if appropriate | 2 | 2 | - | - | - | - | - | - | - |
| 7. Results | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 |
| • Measure of effect for outcomes and appropriate measure of precision | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Adequacy of follow-up for each study group | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 8. Discussion | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Conclusions supported by results with possible biases and limitations taken into consideration | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| 9. Funding or Sponsorship | 5 | - | 4 | 4 | 4 | - | 4 | - | 2 |
| • Type and sources of support for study | | - | 4 | 4 | 4 | - | 4 | - | 2 |
| TOTAL SCORE | 100 | 64 | 66 | 78 | 64 | 63 | 67 | 67 | 60 |

Table 7 cont.. *Methodological quality of observational studies for chronic non-cancer pain.*

| CRITERION | Weighted Score | Deer et al, 2004 (22) | Deer et al, 2002 (69) | Dominguez et al, 2002 (71) | Rainov et al, 2001 (73) | Roberts et al, 2001 (75) | Anderson and Burchiel, 1999 (67) | Winkelmüller & Winkelmüller 1996 (79) |
|---|---|---|---|---|---|---|---|---|
| 1. Study Question | 2 | - | 2 | 2 | 2 | 2 | 2 | 2 |
| • Clearly focused and appropriate question | 2 | - | 2 | 2 | 2 | 2 | 2 | 2 |
| 2. Study Population | 8 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Description of study population | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 4 |
| • Sample size justification | 3 | - | - | - | - | - | - | - |
| 3. Comparability of Subjects for All Observational Studies | 22 | 11 | 5 | 12 | 5 | 3 | 9 | 3 |
| • Specific inclusion/exclusion criteria for all groups | 5 | 2 | 5 | 5 | 5 | 3 | 3 | 3 |
| • Criteria applied equally to all groups | 3 | 2 | - | 3 | - | - | 3 | - |
| • Comparability of groups at baseline with regard to disease status and prognostic factors | 3 | 2 | - | 1 | - | - | - | - |
| • Study groups comparable to non-participants with regard to confounding factors | 3 | 2 | - | - | - | - | - | - |
| • Use of concurrent controls | 5 | - | - | - | - | - | - | - |
| • Comparability of follow-up among groups at each assessment | 3 | 3 | - | 3 | - | - | 3 | - |
| 4. Exposure or Intervention | 11 | 11 | 8 | 11 | 8 | 8 | 8 | 8 |
| • Clear definition of exposure | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| • Measurement method standard, valid and reliable | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| • Exposure measured equally in all study groups | 3 | 3 | - | 3 | - | - | - | - |
| 5. Outcome measures | 20 | 14 | 13 | 15 | 12 | 12 | 15 | 14 |
| • Primary/secondary outcomes clearly defined | 5 | 5 | 5 | 5 | 4 | 4 | 5 | 4 |
| • Outcomes assessed blind to exposure or intervention | 5 | - | - | - | - | - | - | - |
| • Method of outcome assessment standard, valid and reliable | 5 | 4 | 3 | 5 | 3 | 3 | 5 | 5 |
| • Length of follow-up adequate for question | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 6. Statistical Analysis | 19 | 11 | 4 | 4 | 5 | 5 | 8 | 5 |
| • Statistical tests appropriate | 5 | 5 | 4 | 11 | 5 | 5 | 5 | - |
| • Multiple comparisons taken into consideration | 3 | 3 | - | 3 | - | - | 3 | - |
| • Modeling and multivariate techniques appropriate | 2 | - | - | 2 | - | - | - | - |
| • Power calculation provided | 2 | - | - | - | - | - | - | - |
| • Assessment of confounding | 5 | 3 | - | - | - | - | - | - |
| • Dose-response assessment if appropriate | 2 | - | - | 2 | - | - | - | - |
| 7. Results | 8 | 8 | 7 | 8 | 6 | 7 | 8 | 8 |
| • Measure of effect for outcomes and appropriate measure of precision | 5 | 5 | 4 | 5 | 3 | 4 | 5 | 5 |
| • Adequacy of follow-up for each study group | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 8. Discussion | 5 | 5 | 4 | 5 | 5 | 4 | 5 | 4 |
| • Conclusions supported by results with possible biases and limitations taken into consideration | | 5 | 4 | 5 | 5 | 4 | 5 | 5 |
| 9. Funding or Sponsorship | 5 | - | 5 | - | 2 | 4 | - | 5 |
| • Type and sources of support for study | | - | 5 | - | 2 | 4 | - | 5 |
| TOTAL SCORE | 100 | 65 | 53 | 62 | 50 | 50 | 60 | 53 |

Table 8. *Summary descriptions of studies for intrathecal drug delivery for cancer-related pain.*

| Study / Methods | Participants | Intervention | Outcome | Results | Conclusion(s) Short-term <1 year | Complications |
|---|---|---|---|---|---|---|
| Rauck et al, 2003 (74) | 149 patients were enrolled, 119 implanted for refractory cancer pain (analgesic doses caused intolerable side effects) with implanted ITP for morphine therapy-trialed with percutaneous bolus injection with at least 50% improvement in pain, device activated at 14 days post implant | Implantable drug infusion system with morphine; self titration of systemic opioids | Outcomes included supplemental opioid use, opioid complications, pain relief, success was defined as 50% or > reduction in one of the aforementioned 3 and global assessment | NAS decreased 31% and was maintained through months 10-13 in 15 patients, systemic opioid use at 13 months was 0%; opioid complication data not available for 13 months, rating was excellent in 87% of patients at 13 months | IT morphine can decrease opioid side effects, systemic medications, and improve VAS and patient satisfaction at one year in patients with refractory cancer pain | Of the 119 implants, 7 patients had device related malfunctions, 36 had procedure related complications, one had event related to intercurrent illness or injury (40 patients total)<br>Of the 119 cancer pain patients implanted, 15 made it to 13 months |
| Smith et al, 2002 (83) | 202 patients enrolled with refractory cancer pain, multicenter trial with initial VAS > or = 5 despite 200mg/d oral morphine equivalent, age >18, life expectancy > 3 months; most had mixed neuropathic and nociceptive pain (60%); baseline VAS approximately 7.5 | Implanted IDDS to manage refractory cancer pain as compared to CMM | Prospective multicenter randomized study, data collected baseline 2, 4, 6, 8, 10, 12 weeks; primary evaluation was 4 weeks after randomization comparing CMM with IDDS; measured VAS, toxicity, secondary outcomes: individual drug toxicities, quality of life, health care resource, mortality, opioid dose | 60/71 IDDS patients achieved success, as compared to CMM 51/72 patients, IDDS patients had decreased VAS of at least 2 points and toxicity (41/71) vs 27/72 with CMM; IDDS decreased 52%, as compared to 39% reduction, further IDDS survivability was better than CMM (53.9 vs 37.2) | IDDS improved pain control, reduced toxicity and improved survival in patients with refractory cancer pain. | 194 serious adverse events reported, split evenly among the 2 groups (CMM 95 IDDS 99). 16 were associated with implanted pump or "related procedure," of these 6 were related to the pump, 5 to lumbar insertion site, and 5 to the catheter; surgical revision required in 10, explanted in one because of infection |
| Becker et al, 2000 (80) | 43 consecutively treated cancer patients, 19 female and 24 male, with a mean age of 64 years (range: 40–84 years) | In only 19 patients was a screening trial performed mostly through an epidural catheter | VRS, best pain reduction, final pain reduction | Neuropathic pain reduction (VRS was 61.1%, nociceptive pain was 77.8%; longer duration of nociceptive pain reduction. No more than moderate pain reduction was recorded in patients with peripheral nerve involvement, nervus plexus avulsions, and spinal cord compression did not show any long-term benefit of intrathecal opioid application | IT morphine is an effective treatment for neuropathic and nociceptive cancer pain. Best results were observed for nociceptive in the "trunk area of the body." | Complications from pump in 5 patients: 3 spinal catheter malfunction, pump pouch hematoma, post-operative pneumonia. No malfunctions of hardware or local infection was reported. |
| Onofrio and Yaksh 1990 (82) | 53 patients with terminal metastatic disease; 24 males, 29 females, mean age 58 years, median age 62 years | Trialed with single shot morphine IT trial 0.5 to 2 mg) and IDDS with morphine for terminal cancer pain, analgesic effects, prognostic value of trial to infusion success | Parenteral narcotic use, analgesic index, mobility, overall outcome | Analgesic index improved, mobility improved, 26 patients had therapy for at least 16 weeks, week 16 IT infusion was 9.5 ±2.1mg/d, compared to 3.7 ±0.3mg/d, 65% self-reported good or excellent results | Long-term efficacy and safety of spinal opioid infusion in patients with terminal cancer is justified. | Miscalculation of pump refill dates leading to severe pain in 5 cases, in one autopsy of patient with dose of 24mg/d, no granuloma seen at 130 weeks |
| Penn and Paice 1987 (81) | 35 patients with intractable cancer pain, implanted with IDDS, 8 with nonmalignant pain | Intrathecal morphine infusion | Relief measured by self-reported NRS, enteral opioid consumption, self-report increase daily activities, mean follow-up 5.4 months for cancer patients | 17/35 patients reported 0-3 on NRS and >50% reduction of opioids with significant increase activities, 11 reported VAS 4-6 with < 50% decrease opioids and some activity improvement; 80% of patients had either good or excellent relief | Data supports use of chronic IT morphine for treatment of intractable malignant pain | No associated morbidity or mortality was associated with pump implantation or infusion. |

IDDS = Intrathecal drug delivery system; CMM = Conservative Medical Management; VRS = Verbal Rating Scale; NAS = Numeric Analog Scale; NRS = Numeric Rating Scale; IT = Intrathecal

*Table 9. Summary description of observational studies for intrathecal drug delivery in non-cancer pain.*

| Study / Methods | Participants | Intervention | Outcome | Results | Conclusion(s) Short-term <1 year Long-term ≥1 year | Complications |
|---|---|---|---|---|---|---|
| Atli et al, 2010 (68) | 57 patients spanning 5 diagnostic groups: FBSS (28), neuropathic pain (16), malignancy (2), visceral pain (5), miscellaneous (6), 49 included in study, 43 at 3 year follow-up | Implantation of IDDS for pain | Self-reported pain scales (VAS), complications, IT, and systemic opioid consumption | VAS reduced 7.7 to 5.7 at 3 years, along with systemic opioid consumption mean from 183mg/day morphine equivalents to 57.6mg/ day at 3 years, along with gradual increases in IT doses of 6.5mg/day to 12.2mg/ day, pre-implant opioid consumption inversely correlated with treatment success | ITP therapy produces long-term reductions in pain severity scores and oral opioids consumption. | Complication rate 20%, 14 complications occurred in 10 of 57 patients: 5 with wound infection, 2 with IT granuloma, 2 with seroma at pump site, 3 with catheter migration fracture. Treatment failure rate 24%. |
| Duse et al 2009 (20) | 30 patients with chronic nociceptive, neuropathic or mixed non-cancer pain that failed multimodal analgesic regimens (opioids, neuropathic pain medications, NSAIDs), patients had pain for at least 30 months, average age 64 year old, weaned off opioids prior to trialing with epidural morphine x 3 wks | IDDS therapy with morphine with dose adjustment to maintain > 50% reduction of initial value | At 0, 3, 12, and 24 month intervals after implant and evaluated by self-reported VAS, MPQ | MPQ improved 66%, theeffective component 59%, and the sensory component 32%. VAS improved by 55%. The average morphine infusion rate increased to 0.80±0.45 mg/day at the 24-mo follow-up intervals (P _ 0.05). Among 13 patients of working age, 12 returned to work full time. | IT infusion of morphine using IDDS was helpful in improving psychosocial function and improved pain scores in patients that have failed multimodal therapy. | None reported |
| Ellis et al, 2008 (72) | 155 patients with severe chronic pain (107 non-cancer pain and 48 with cancer related pain) from one of 2 RCT demonstrating response; 31 patients participated in study > 12 months, mean was 288 days | Implanted infusion systems and external micro infusion pumps for cancer pain patients. Ziconotide only therapy offered. | At 1, 6, 12 months functional capacity and QOL scores (PDI and SIP-20 for patients from non-cancer pain) RTC vs. Karnofsky Performance at screening, twice during first 30 days, and then monthly for cancer pain; PDI, SIP-20 and VASPI for descriptive statistics; safety analysis was descriptive COSTART for AE | 61/155 (39.4%) stopped because of AE, 31/155 were followed for at least a year, post-hoc analysis of retained patients demonstrated no attenuation of analgesic affect and stable dose through 12 months (P<0.0001); PDI and SIP-20 not carried beyond one-month; VASPI went from 77.9 to 43.6 with mean % reduction of 45.8 | Post-hoc analysis of retained patients demonstrated no attenuation of analgesic effect of mean % reduction of VASPI by 45.8 and stable dose through 12 months (P<0.0001); | Ziconotide related AE occurred in 147/155 patients; 39.4% discontinued treatment because of AE, most common being confusion at 43.2% |
| Ilias et al 2008 (21) | 168 patients with existing (79 patients) or recently implanted IDDS (89 patients) with unpredictable pain fluctuations with non-cancer (92%, most common FBSS) and cancer pain (8%), mean age 56.4 years, 58% female, 119 patients had data at 12 months | Given personal therapy manager (PTM) options via SynchroMed EL or SynchroMed II pumps | Baseline visit, screening and implant visit for patients without previous IDDS, a PTM start visit, and follow-up at 12 months measuring VAS, EQ-5D, medications, VAS, PTM settings, adverse events, and self report satisfaction | At 12 months, patients with existing IDDS, VAS decreased from 6.4 to 5.5 at 12 months, in newly implanted group, VAS decreased from 8.0 to 4.1. Most common IT drug was morphine (66% at 12 months), PTM at 12 months was 170 sec, lockout 2 hours, max/day 5 boluses, average PTM per days 1.3 at 12 mo; all patients tended to decrease the concomitant pain medication and the QOL tended to improve (10% on the EQ-5D scale). In total, 85% of patients were satisfied with the PTM device. | Patient controlled analgesia with PTM is viable and effective method to treat patients with intractable pain and improves control over unpredictable pain fluctuations. | 181 complications occurred in 92 patients, 32% were benign and drug related side-effects, 16 were related to pump related events that resolved after reprogramming. No serious adverse events occurred. |

*Table 9 cont. Summary description of observational studies for intrathecal drug delivery in non-cancer pain.*

| Study / Methods | Participants | Intervention | Outcome | Results | Conclusion(s) Short-term <1 year Long-term ≥1 year | Complications |
|---|---|---|---|---|---|---|
| Shaladi et al, 2007 (76) | 24 patients with osteoporosis with presence of chronic vertebral compression fracture, VAS >7 after failed conservative therapy for 3 months, failed systemic opioid therapy, drug addition, and absence of barriers with successful trial | IT morphine after successful trial of >50% pain reduction with trial of morphine (0.5 to 1 mg) | VAS, QUALEFFO (Quality of Life Questionnaire of the European Foundation of Osteoporosis), and morphine dose at one year post implant | VAS declined from 8.7 pretrial to 1.9 one year later, the QUALEFFO dropped from 114.7 to 79.1 one year post implant. Mean IT morphine dose at one year was 16.32 mg/day. Patients reported improved function and satisfaction with therapy, also no systemic opioid medications | IT morphine relieves pain and improves QOL, in patients with severe osteoporosis. | One wound infection, one delayed wound healing, nausea, and itching |
| Staats et al, 2007 (77) | 101 consecutive patients with IDDS from 8 different centers (no more than 20 per center) implanted for management of chronic intractable non-cancer back pain with therapy for at least 2 years | IDDS therapy with opioids, local anesthetics, adjuvants, or combination thereof for at least 2 years | Outcomes were time to initiation of constant flow treatment (either simple continuous, single bolus + simple continuous), number of program adjustments, medications used | Most pumps had morphine (47.7%); pre-implant pain score in 89 patients was 7.7, refill visits averaged every 1.5 months, 34% had single medication therapy, 35.6% had 2 medication therapy, 89% had daily morphine no greater than 25mg/day, 56.9% had concentration of < 25mg/cc; 94% had constant flow treatment, maintained from 1-3 months to >30 months post implant (mean initiating was 2.7 month) | Data suggests that patients with non-cancer pain could be implanted with constant flow rate pump and can be maintained throughout treatment | None reported |
| Doleys et al, 2006 (70) | Patients with non-cancer pain, primarily in lumbar back and /or legs s/p FBSS, with pretreatment pain at least 2 years in duration, intrathecal therapy (50) after 2 week epidural trial with at least 50% improvement in pain, systemic opioid therapy (40), and residential pain/rehabilitation program (40), all of which resided within Birmingham, AL. | IT therapy was morphine, hydromorphone, or fentanyl ± local anesthetic | NRS, ODQ, Beck Depression Inventory, MPQ, health related QOL, and SF-36, work status, and patient opinion measures for 4.2 years (IDDS), 4.3 years (rehab), and 4.8 years (systemic opioid therapy) | The IDDS group appeared superior to the other 2 groups, with the NRS with the greatest change (7.9 to 5.12), while the systemic opioid group reported overall satisfaction better while the rehab group reported highest quality of well being score. | There appeared to be a disconnect between QOL, pain, disability, and mood, and the IDDS group appeared o report greatest improvement. | None reported |
| Thimineur et al, 2004 (78) | 69 non-cancer pain patients with pain determined as severe, conservative treatment failure, divided into 2 groups. 38 pts. received intrathecal pump, 31 did not (patients with unsuccessful trial or declined intrathecal therapy) and were followed as NR. Another group of new patients (n = 41) used as comparative group NR (non-recipient group). | Intrathecal morphine, hydromorphone, fentanyl, Clonidine, Baclofen, bupivacaine, and methadone. Non intrathecal group continued the pre-study medications (systemic opioids). | Multiple questionnaires – symptom checklist 90-R, SF-36 Health study, Beck depression questionnaire, MPQ – short, Oswestry disability index, Pain drawing, VAS (1-10). Evaluations done at baseline and then every 6 months for 3 years. | 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 baseline 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. | Intrathecal opioid therapy for non-cancer pain should be considered appropriate only when all other conservative medical management options have been exhausted. | Pocket infection in 2, one had kinking of catheter; one patient had transverse myelitis picture with continued motor deficiency |

*Table 9 cont. Summary description of observational studies for intrathecal drug delivery in non-cancer pain.*

| Study / Methods | Participants | Intervention | Outcome | Results | Conclusion(s) Short-term <1 year Long-term ≥1 year | Complications |
|---|---|---|---|---|---|---|
| Deer et al, 2004 (22) | Multicenter prospective registry of 136 patients with chronic low back pain > leg pain | Implantable drug infusion systems delivering opioid following successful trial. 81.1% were trialed with morphine only | Outcome measures: Numeric Pain Ratings and Oswestry scores, secondary outcomes amount of medications via other routes and return to work | Significant improvements in numeric pain ratings and Oswestry scores at 6 and 12 months. Few patients who had successful trials but were not implanted did not improve. Patients with neuropathic pain had a statistically significantly lower trial success rate. There was a decrease in oral opioids and maintenance or improvement in work status in implanted patients. | At 12 months, patients implanted had significant improvement in pain and Oswestry scores and a high satisfaction rate | 23 patients had adverse events with IIDS, 21 required surgery for correction: infection (2.2%), migration (1.5%), CSF leak (0.7%), catheter kinking (1.5%), and catheter fracture (0.7%), reaction to medication (5.1%).All resolved without untoward events. |
| Deer et al, 2002 (69) | 109 consecutive patients for bupivacaine + opioid compared with opioid alone, 84 non-cancer patients and 25 cancer patients | Implantable drug infusion systems delivering opioid alone vs opioid + bupivacaine | 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. | With combination (bupivacaine + opioid) infusion the pain relief was significantly better, the number of oral opioids used were significantly less, number of oral non-opioid 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. | 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. | Medication related side effects, including non-dermatomal numbness, peripheral edema, summarily: no long-term effects associated with IT therapy |
| Dominguez et al, 2002 (71) | Retrospective study of implanted patients at a tertiary center. 157 patients screened, 134 implanted, of whom 86 were available for follow up | All patients received IT bolus trials with morphine starting at 0.5 mg. Those who did not respond, were given 1 mg or more boluses (high responders). Patients were implanted with morphine initially. | Dose escalation comparison between high responders vs. standard/low dose responders, dose escalation with respect to gender, age, and underlying pain condition | High responders had a disproportionate increase in opioid requirements. Hydromorphone replaced morphine or adjuvants were added in half the cases by 18 months. Women and individuals older than 65 years had lower opioid requirements 18 months or more post-implant. | The degree of responsiveness to an intrathecal narcotic during a trial period, along with the patient's age and gender, have predictive value on the long-term utilization of IT analgesics in chronic non-cancer patients. | Poor patient tolerance of the implantable device, intolerable side effects, infection, or failure to achieve acceptable pain relief led to removal of the device in 17 patients of the original 134 implanted. 31 patients followed up care elsewhere. |
| Rainov et al, 2001 (73) | 26 patients, median age 54 years, s/p FBSS and failed conservative management; 18 of which had neuropathic/ nociceptive pain, 6 with radicular, and 2 with radicular peripheral neuropathic; nondermatomal | Intrathecal morphine/ clonidine or morphine/ bupivacaine or morphine/ bupivacaine/ clonidine, or morphine/ clonidine/ bupivacaine/ midazolam | Mean follow-up was up to 27 months, data collected 2 years: VAS, and non-formal self-report of daily activities, including walking, sleep, systemic medications, motor disturbances, sensory disturbances, and bladder control, dose of IT morphine per day, and patient global rating of therapy | VAS maintained at one month following implant to 2 years from 8 to 50% improvement; most patients reported improvement in walking ability, reduction systemic pain medications, and sleep; mean daily dose of morphine alone or in combination was 6.2 ±2.8mg morphine, 2.5 mg ±1.5mg bupivacaine, 0.06mg ± 0.03mg for clonidine, and 0.8mg ± 0.4mg for midazolam; 73% rated long-term treatment as excellent or good. | Intrathecal polyanalgesia employing morphine alone or in combination with non-opioid drugs can have a favorable and sustained analgesic efficacy in patients with complex chronic pain of spinal origin, with lack of major drug-related complications. | 3/26; 2 device occlusion of catheter and leakage; one human error during refilling causing leak of medication from reservoir septum |

*Table 9 cont. Summary description of observational studies for intrathecal drug delivery in non-cancer pain.*

| Study / Methods | Participants | Intervention | Outcome | Results | Conclusion(s) Short-term <1 year Long-term ≥1 year | Complications |
|---|---|---|---|---|---|---|
| Roberts et al, 2001 (75) | 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 (n=5), cervical failed spinal surgery (n = 4), crush fractures (n = 3), chronic pancreatitis (n = 3), others (n = 12). | Intrathecal opioids (morphine) via implantable drug administrations systems after a successful trial | Global pain relief, physical activity levels, medication consumption, work status, intrathecal opioid side-effects, proportion of patients who ceased therapy, and patient satisfaction | 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. | 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. | Technical complications occurred with the drug administration device, predominantly catheter related, requiring at least one further surgical procedure in 32 patients (40%). |
| Anderson and Burchiel, 1999 (67) | 40 consecutive patients with non-cancer pain, 58% women, 47% had FBSS; 30 had a successful trial and were implanted. 50% of patients had mixed neuropathic-nociceptive and 33% had peripheral neuropathic pain | 14 patients were screened by single injection of 1 mg morphine intrathecally. 26 patients had 2-3 day trial of epidural morphine infusion by external pump. Patients with ≥ 50% pain relief were implanted with IDDS (10/14 and 20/26 respectively) with either morphine, hydrocodone, or in combination with bupivacaine | VAS and MPQ and the Chronic Illness Problem Inventory | Data was available on 20 out of the 27 surviving patients at 24 months. VAS scores were significantly decreased over baseline at each reporting interval for the entire 24 months of follow-up. 50% of patients reported ≥ 25% pain relief at 24 months post-implant. | Continuous intrathecal morphine can be a safe, effective, and sustainable therapy for the management of severe, non-cancer pain among carefully selected patients. | No infections. 2 patients had PDPH, 5 had device related complications requiring repeat operation, pump malfunction x2 patients, one programming error, pharmacologic complications resolved within 3 months of therapy |
| Winkelmüller & Winkelmüller 1996 (79) | 120 patients with non-cancer pain followed from 6 mos. to 5.7 yrs. Patients had nociceptive–neuropathic pain due to multiple lumbar spinal operations. | 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. | Outcome measurement with VAS and MPQ, level of activity, mood, QOL, complications and side effects | 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). | Long-term administration of spinal opioid medications for non-cancer 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. | 14 pumps had to be replaced for technical reasons, including irregular flow rates, skin perforations, or refilling errors; in all 31 of 120 were considered treatment failures. |

MPQ = McGill Pain Questionnaire; QOL = Qualityquality of Lifelife; FBSS= Failed Back Surgery Syndrome; VAS = Visual Analog Scale; ITP = Intrathecal Pump; IDDS = Intrathecal Drug Delivery System: IT = Intrathecal; AE = Adverse Events; NSAID = Non-Steroidal Anti-Inflammatory Drug; QOL = Quality of Life; SIP = Sickness Impact Profile; PDI = Pain Disability Index; VASPI = Visual Analog Scale of Pain Intensity; COSTART = Coding Symbols for Thesarus of Adverse Reaction Terms; PTM = Personal Therapy Manager; EQ-5D = EuroQoL Questionnaire; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis

(20) prospectively evaluated the effects of chronic intrathecal morphine delivery on emotional variables affecting pain perception and functioning in patients with severe chronic non-cancer pain involving the low back and/or lower extremities. Of 42 patients evaluated, 30 were implanted with IDDS after a successful epidural morphine infusion trial. All patients were taking opioids prior to enrolling in the study and received only morphine intrathecally, were followed for 24 months, and were administered serial MPQ. VAS scores were significantly improved at all time intervals studied compared to baseline. Significant progressive improvements were noted in the affective, evaluative, sensory, and mixed components of the MPQ. Good to excellent satisfaction was reported in 29 of the 30 implanted patients; activities of daily living were improved in 26 patients and 12 patients were able to return to full-time employment. No significant complications were noted. A more recent study by Atli et al (68) retrospectively examined charts of 57 patients, 55 with non-cancer pain. About half had a diagnosis of "FBSS" and 16 patients had neuropathic pain. Patients were trialed using a continuous intrathecal infusion with morphine and infrequently with hydromorphone or sufentanil and titrated over a 5-day period. Patients were implanted with the same solution if they achieved satisfactory pain relief at the end of the trial period. Patients were followed for 3 years from implant. Eight patients were excluded; 3 because of death (including the 2 cancer pain patients), 2 for relocating to a different geographical area, 2 for pump infection/revision, and one patient was excluded for being an "outlier." There was a statistically significant decrease in VAS pain scores at one, 2, and 3 years post-implant. However, a clear trend of temporal decrease in percentage of patients with > 50% pain relief and those with > 30% pain relief emerged, such that by the end of 3 years post-implant 18% of patients experienced > 50% pain relief and 37% had > 30% pain relief. However, oral opioid consumption was decreased significantly throughout the 3-year follow-up and 24% of patients had ceased all oral opioid consumption. Of note, higher initial oral opioid consumption was correlated with lower likelihood of long-term pain relief with intrathecal opioids. No adjuvant intrathecal medications were allowed and the intrathecal opioid requirements in morphine equivalents per 24-hour increased from 6.5 mg at baseline to 12.2 mg at 3-years, an 88% increase. Complications included infection in 5 patients, 3 catheter revisions, 2 intrathecal granulomas, and 2 pocket seromas. Summary results of non-cancer pain studies are displayed in Table 10.

Only 5 cancer-related pain studies were identified and the study characteristics are described here. Smith et al (83) performed a randomized, controlled study comparing comprehensive medical management (CMM) to IDDS for intractable mixed neuropathic and nociceptive refractory cancer related pain. Refractory cancer pain was defined as patients reporting a VAS score greater than or equal to 5 despite 200 mg/day oral morphine equivalents. Success was defined as improvement in VAS or reduction in toxicity as primary outcomes; 60/71 IDDS patients achieved success, as compared to 51/72 CMM patients. Further, this randomized trial demonstrated greater survival at 6 months in patients receiving IDDS. Drug related toxicities were less in the IDDS group compared to the CMM group and were especially significant for reductions in fatigue and depressed level of consciousness. A total of 194 serious complications were reported, split evenly between the 2 groups. Of the 99 complications in the IDDS arm, 16 were related to the "implanted pump or related procedure," 10 requiring revision and one requiring explant (83). A prospective cancer pain study by Rauck et al (74) followed patients for over a year. In that study, 119 patients were implanted with an investigational patient-activated internalized intrathecal morphine delivery system. This study showed that patients with inadequately controlled cancer pain or having intolerable side effects achieved better analgesia when managed with this patient-activated intrathecal morphine bolus delivery device. However, significant complications were noted related to device function and/or procedure and the device did not receive FDA approval (74). Additionally, of the 119 cancer pain patients implanted, only 15 made it to 13 months. Hence, for cancer pain studies, a lesser duration of follow up than one year is more reasonable. Becker et al (80) retrospectively reviewed 43 consecutive patients with neuropathic, nociceptive, and mixed cancer-related pain who were treated with intrathecal opioid therapy. Data regarding pain response via numerical rating scale, intrathecal dose, and pain relief relative to type and location of pain were collected. Neuropathic pain and nociceptive pain was reduced in initial stages, as measured by the numerical rating scale, of 61.1% and 77.8%, respectively. It was noted that in later stages of the therapy, pain relief was significantly less in neuropathic pain than in nociceptive pain. Reported complications of IDDS were discovered and treated in 5 patients (none related to malfunction of hardware or local infection, 3 had spi-

Table 10. *Summary results of eligible non-cancer pain studies included in this systematic review.*

| Study | Study Characteristics | Methodological Quality Scoring | Number of Participants | ≥ 30% Pain Relief | | ≥ 50% Pain Relief | | Results | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 6 mos. | ≥12 mos. | 6 mos. | ≥12 mos. | Short-term < 6 mos | Long-term ≥ 12 mos |
| Atli et al, 2010 (68) | Observational Retrospective | 64 | 43 | | x | | | | x |
| Duse et al, 2009 (20) | Observational Prospective | 66 | 30 | | | | x | | x |
| Ellis et al, 2008 (72) | Observational Prospective | | 155 | | x | | | | x |
| Ilias et al, 2008 (21) | Observational Prospective | 64 | 168 | | x | | | | x |
| Shaladi et al, 2007 (76) | Observational Prospective | 63 | 24 | | | | x | | x |
| Staats et al, 2007 (77) | Observational Retrospective | | 101 | | x | | | | x |
| Doleys et al, 2006 (70) | Observational Retrospective | | 180 | | x | | | | x |
| Thimineur et al, 2004 (78) | Observational Prospective | 60 | 69 | | x | | | | x |
| Deer et al, 2004 (22) | Observational Prospective | 65 | 136 | x | x | | | x | x |
| Deer et al, 2002 (69) | Observational Retrospective | 53 | 109 | | | | x | | x |
| Dominguez et al, 2002 (71) | Observational Retrospective | 62 | 86 | | | | x | | x |
| Rainov et al, 2001 (73) | Observational Prospective | 50 | 26 | | | | x | | x |
| Roberts et al, 2001 (75) | Observational Retrospective | 50 | 88 | | | | x | | x |
| Anderson and Burchiel, 1999 (67) | Observational Prospective | | 40 | | x | | | | x |
| Winkelmüller & Winkelmüller 1996 (79) | Observational Retrospective | 53 | 120 | | | | x | | x |

nal catheter challenges) (80). Onofrio and Yaksh (82) investigated characteristics of intrathecal morphine analgesia in terminal metastatic disease. The median post-implant survival time was 4 months. Morphine was exclusively used for the trial and the infusion. An analgesic index was calculated at trial time and consisted of duration of pain relief in hours x magnitude of relief/ morphine dose in mg. Endpoints of the study included parenteral narcotic use, analgesic index, mobility, and overall outcome and prognostic value of the trial to infusion success. At 16 weeks post infusion, the average dose of intrathecal morphine was 9.5 ± 2.1 mg/d compared to 3.7 ± 0.3mg/d at 2 weeks. Sixty-five percent of 26 patients with infusions that exceeded 26 weeks self-reported good or excellent results, while all 53 patients had improved analgesic index and mobility improved. Furthermore, patients that with a low analgesic index at trial were noted to require rapid dose escalation and that correlated with poor overall outcome, suggesting utility of the index in a standard trialing method. Miscalculation of pump refill dates led to severe pain in 5 cases (82). Penn and Paice (81) investigated pain relief by self-reported NRS, enteral opioid consumption, and self-reported daily activity logs in 43 patients, 35 of whom had intractable cancer pain. Patients were asked to categorize pain as excellent (0-3 on 0-10 NRS, greater than 50% reduction of oral narcotics, with significant increase in daily activities), good (4-6 on NRS, less than 50% reduction in oral narcotics, and some improvement in activities) to poor and failure. Seventeen of 35 cancer patients had excellent results based on the above criteria, while 80% had good or excellent results. No complications were attributed to the hardware or the infusion (81). Summary results of cancer-related pain studies are displayed in Table 11.

Systematic reviews on intrathecal drug delivery for

pain have been performed by several groups (24,29,98-101), including organizations that attempt to make recommendations in regard to reimbursement/coverage (98). The methodologies utilized varied significantly. On one end of the spectrum, case reports were allowed, and on the other end, only long-term assessments with specific documentation of indications and medications utilized. All of the reviews recognize that there is a paucity of good quality publications for intrathecal infusion therapy, especially for chronic, non-cancer pain. While the literature has significant heterogeneity of patient types, medications, and devices, there appears to effectiveness in regard to pain relief. The details of systematic reviews on intrathecal therapy for pain are detailed in Table 12. However, there is insufficient information for adequate comparison to other routes of

Table 11. *Summary results of eligible cancer pain studies included in this systematic review.*

| Study | Study Characteristics | Methodological Quality Scoring | Number of Participants | ≥ 30% Pain Relief | | ≥ 50% Pain Relief | |
|---|---|---|---|---|---|---|---|
| | | | | 3 mos. | ≥6 mos. | 3 mos. | ≥6 mos. |
| Rauck et al, 2003 (74) | Observational Prospective | 60 | 149 | x | x | | |
| Smith et al, 2002 (83) | Randomized Controlled Trial | 64 | 202 | | | x | x |
| Becker et al, 2000 (80) | Observational Retrospective | 53 | 43 | x | NA | x | NA |
| Onofrio and Yaksh, 1990 (82) | Observational Prospective | 62 | 53 | | NA | x | NA |
| Penn and Paice, 1987 (81) | Observational Retrospective | 60 | 43 | x | NA | x | NA |

Table 12. *Summary description of systematic reviews for intrathecal drug delivery.*

| Systematic Review | Inclusion Criteria | Exclusion Criteria | Number of Studies/ Patients | Outcome Measures | Outcomes | Complications | Conclusions |
|---|---|---|---|---|---|---|---|
| Patel et al, 2009 (24) | Fixed rate or programmable intrathecal infusion pump studies for chronic non-cancer pain. Specific indication for intrathecal infusion and drug utilized Minimum 12 months duration Clear documentation of outcomes and complications Minimum patient number = 25 | Lack of clear documentation of infusion systems or mixed delivery methods Externalized infusion systems for short-term use Less than 12 months follow-up Lack of clear documentation of indications and patient population being studied | 4 observational studies, 386 patients | Primary outcome: > 50% relief<br><br>Secondary outcomes: improvement of function, reduction in amount of oral medication, decrease in side effects from systemic drugs, improvement in quality of life | 2 studies were positive for efficacy, one was negative, one study was not applicable | Not assessed | Intrathecal infusion devices for chronic non-cancer pain have positive long-term outcomes and a role as an advanced-stage therapy, based on limited studies |
| Noble et al, 2008 (98) | English language Controlled trials and uncontrolled long-term case series. Prospective and retrospective. Chronic non-cancer pain. Minimum of 10 implanted infusion pump patients Minimum of 6 months for efficacy data | Outcomes requiring patients to remember their previous health | 16 studies, 2081 patients | 25% and 50% pain relief. Discontinuation from trial due to insufficient pain relief. Quality of Life (Tollison , SF-36, and QUALEFFO). Functional status. Employment status. Use of other medications or treatments. Change in medication over time. Discontinuation due to AEs. MAUDE reports. Cost | 25% relief: 56.3%. 50% relief: 40.8%. Inadequate relief discontinuation: 8%. Quality of life: inconsistent findings. Functional status and Employment status: insufficient quantity of evidence. Use of other medications: Overall decrease. Dose of medication increased over time but quantity is not predictable. Discontinuation from AEs: 8.3% | Reoperation: 9%-42%. PDPH 0%-31%. Pump failure: 0%- 8% Seroma: 0%-6%. No serious drug related adverse events | Effectiveness data of IT pumps for chronic non-cancer pain only from uncontrolled case series. Inconsistent findings among studies for pain relief. Inadequate data for conclusions of QOL or functional status. Adverse events included reoperation but difficult to conclude mean incidence. |

Table 12 (cont.). *Summary description of systematic reviews for intrathecal drug delivery.*

| Systematic Review | Inclusion Criteria | Exclusion Criteria | Number of Studies/ Patients | Outcome Measures | Outcomes | Complications | Conclusions |
|---|---|---|---|---|---|---|---|
| Turner et al, 2007 (29) | 1) English language journal article,<br>2) Intrathecal opioid or ziconotide via programmable pump,<br>3) Patient diagnoses not limited to spasticity or specific diseases<br>4) Original data on pain, functioning, or complications in humans | 1) Constant flow pumps or unknown type of pump<br>2) >10% were treated for spasticity or a specific disease<br>3) Study only focused on patients who failed the first IT drug received<br>4) Case reports | 6 observational articles met criteria for effectiveness and complication review, additional 4 met criteria for complication review only<br><br>Effectiveness: 342 trialed, 258 implanted<br>Complications: 377 trialed, 342 implanted | Effectiveness: pain (VAS and NRS) and functioning (CIPI and Oswestry)<br>Complications: a- biologic, b- hardware related<br>Follow up was over 3-60 months | Pain improved on average across all studies, but high attrition rate, and increased opioid consumption over time.<br>All had some improvement in functioning but all had methodology flaws. | Wound infection- 12%, meningitis- 2%, CSF leak -0%, N/V- 33%, Sedation- 2%, urinary retention- 24%, pruritus- 26%, respiratory depression- 0%, sexual dysfunction- 25%, constipation- 38%, catheter related complication -18%, pump failure- 5%, reoperation- 27%, pump explantation- 5% | IT therapy improves pain scores, but increases in medication consumption occur, long-term effectiveness was unclear. Adverse effects were common and often transient. |
| Waara-Wolleat et al, 2006 (100) | Medline search and non-indexed publications (Neuromodulation) Intrathecal fentanyl or sufentanil | 1) Acute clinical use such as preoperative analgesia or for labor | Fentanyl: 2 retrospective analyses, total N = 36, 1 prospective study, N = 69<br><br>Sufentanil: 1 retrospective: N=18 | N/A | Fentanyl and sufentanil were efficacious and tolerated in the majority of patients | Sufentanil did not produce lower extremity edema as opposed to morphine | Limited number of studies with small number of subjects suggest that intrathecal infusion of lipophilic opioids is generally effective and well tolerated, but more studies are recommended. |
| Simpson et al, 2003 (99) | Intrathecal studies Controlled studies and case series included | If duplication of patient data, smaller publication excluded<br>RCTs comparing baclofen versus saline | 1 RCT, 6 case series, 3 cost studies | Pain reduction, composite toxicity score, safety, cost | VAS 1.97 points less than CMM patients<br>Composite toxicity score 2.82 points better than CMM<br>Baclofen had statistically significant improvement in Ashworth score<br><br>Cost difficult to calculate | Surgical revision: 3-17%<br>Pump explantation: 0-21%<br>Catheter complications: 3-10%<br>Dehiscence: 2%<br>Pocket erosion, infection, or seroma: 2.4-4% | Intrathecal infusion for pain and spasticity appears effective for prescreened patients. Therapy appears safe, but drug and device complications do occur and may result in surgical revision. Intrathecal therapy may be less costly than medical management in the long-term. |

delivery. In addition, there is significant lack of data in regard to the multitude of combinations possible between hydrophilic and lipophilic opioids, local anesthetics, clonidine, baclofen, and ziconotide. In regard to safety, drug related adverse effects are mostly transient and well tolerated. Device related complications and need for surgical revision appears to have occurred at a higher rate in earlier publications, and the lower rates in more recent publications may reflect improved education, techniques, and experience in the implanting community. Assessments of cost-effectiveness suggest that cost savings are achieved after 2 years in comparison to systemic pharmacologic therapy for chronic, non-cancer pain (101).

Table 12 (cont.). *Summary description of systematic reviews for intrathecal drug delivery.*

| Systematic Review | Inclusion Criteria | Exclusion Criteria | Number of Studies/ Patients | Outcome Measures | Outcomes | Complications | Conclusions |
|---|---|---|---|---|---|---|---|
| Williams et al, 2000 (101) | Search of Medline, Embase, CancerCD, and PubMed<br>Chronic cancer and non-cancer pain in a hospital, hospice, or community setting<br>Different types of intrathecal pump systems<br>Different types of intrathecal drugs given by pump systems<br>Comparison of intrathecal delivery systems with other routes of analgesia delivery<br>Case series and case reports | Publications that did not specifically measure efficacy<br>Review articles with no original information<br>Studies assessing effectiveness of epidural therapy only<br>Some case series reports excluded for insufficient information of effects and side-effects | 49 reports<br><br>2,571 patients | 1) efficacy measures included: VAS Verbal Rating Score, MPQ, Brief Pain Inventory, range of movement, ability to return to work<br>2) side-effects: (a) pharmacological side-effects (e.g. respiratory depression, effects on motor and/ or autonomic function, nausea and/or vomiting, urinary retention, pruritus); and (b) complications (e.g. local infection, abscess formation, meningitis, bleeding/ hematoma formation, pump pocket seroma, CSF leaks, dural fistula, improper pocket placement, catheter kinking, obstruction, dislodgement, disconnection, malfunction, and pump failure)<br>3) costs: (a) costs of IDDS, including initial costs, maintenance, number of outpatient visits, hospital admissions and use of health care resources; and (b) financial benefits of the pump systems, such as reduction in drug costs, reduction in bed days, quicker return to work, reduction in the use of health service resources (GP visits, outpatient visits) | 1) Efficacy: mean VAS pre-therapy was 7.6 and decreased to 3.0 with IT therapy (16 studies), up to 50% reduction in supplemental analgesia use, 82.5% good to excellent improvement in daily activities, improvement of depression, 77-92% patient satisfaction | Nausea and vomiting: 25%<br>Sedation: 17%<br>Urinary retention: 19%<br>Pruritus: 17%<br>Myoclonic activity: 18%<br>Respiratory depression: 3%<br>Meningitis: 3%<br>Catheter dislodgment: 5-18%<br>Catheter obstruction, kinking<br>Pump failure (battery, rotor stall)<br>CSF leak, seroma | Quality of literature is poor. The heterogeneity of medications, devices, and patient populations make firm conclusions difficult. Efficacy is documented, but insufficient information for comparison to other routes of delivery.<br>Cost information was difficult to assess, but modeling suggests that IT therapy is cost effective after 22 months in comparison to systemic analgesic therapy<br><br>Pharmacologic adverse effects occur in 3-26% and mechanical complications are reported in up to 25% |

NAS = Numeric Analog Scale; VAS = Visual Analog Scale; NRS= Numeric Rating Scale; IT = Intrathecal, IDDS = Intrathecal Drug Delivery System; CSF = Cerebrospinal Fluid; AE = Adverse Events, QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; QOL = Quality of Life; MAUDE = Manufacturer and User Facility Device Experience Database; PDPH= Post-Dural Puncture Headache; CIPI= Chronic Illness Problem Inventory; N/V = Nausea/Vomiting; RCT = Randomized Controlled Trial; N/A = Not Applicable; MPQ = McGill Pain Questionnaire

## Level of Evidence

The evidence for intrathecal infusion systems for non-cancer pain is Level II-3 based on USPSTF criteria. There is Level II-2 evidence for intrathecal infusion systems for cancer-related pain.

### Recommendation

Based on Guyatt et al's criteria (66), the recommendation for intrathecal infusion systems is limited to moderate recommendation for non-cancer pain based on the current moderate evidence derived from randomized and observational studies for chronic c non-cancer pain. The recommendation for cancer-related pain is moderate recommendation based on one high quality randomized controlled trial and evidence from from lesser quality studies.

## Discussion

This systematic review presented evidence on the efficacy of IDDS in the control of cancer and non-cancer related pain. Based on the reviewed evidence, intrathecal therapy is moderately effective and safe in controlling refractory painful conditions that have failed multiple other treatment modalities, both in cancer and non-cancer related conditions. However, there are significant limitations to these inferences.

Significant variability in study design, patient selection, concomitant oral or transdermal opioid use and technical parameters may have important effects on outcomes of intrathecal therapies. Merely having an IDDS implanted does not impart similarity among patients' characteristics or response to therapy. Differences in patient selection, catheter location, medications used, complication rate, and location/type of pain treated may greatly affect outcomes and responses to therapy. Pharmacokinetic characteristics of intrathecally administered medications, particularly lipid solubility, play an important role in analgesic responsiveness. Consequently, the positioning of the catheter can be critical especially with use of lipophilic medications. Most intrathecal agents work by binding to particular receptors in the superficial layers of the dorsal horn. Prior to reaching their targets, intrathecal medications may be taken up by fat tissue and blood vessels. Lipophilic agents are more likely to be taken up by the systemic circulation than hydrophilic agents, as they diffuse easier across cell layers. Hence, hydrophilic opioids such as morphine and hydromorphone are sometimes preferred over hydrophobic opioids as they can diffuse in the CSF and have a higher chance of reaching target areas in the superficial layers of the dorsal horn that may not be immediately adjacent to the catheter tip (102). Unlike other agents used intrathecally, local anesthetics act earlier on sodium channels at the rootlets of nerve fibers (fila radicularia) in the intrathecal space; preferentially over targeting spinal cord receptors (103). Bupivacaine is the predominant local anesthetic used in chronic intrathecal infusion systems and is highly lipophilic. Peripherally generated painful stimuli are conducted along dorsal rootlets entering the dorsal horn of the spinal cord and not ventral rootlets. Hence, a dorsal location of the intrathecal catheter may be advantageous, albeit the dynamics of CSF flow in long-term intrathecal infusions are still undetermined (102,103). None of the studies on intrathecal drug delivery addressed catheter location and only a few have looked at the efficacy of combination of intrathecal medications (13,73,90,104-110). While preservative-free morphine and ziconotide are FDA-approved for the for intrathecal administration for the treatment of chronic pain, a number of other agents including bupivacaine, clonidine, and fentanyl are used often in combination with other agents. The lack of FDA approval for these medications hinders prospective studies and limits the potential to adequately investigate the effectiveness of these agents when used intrathecally, alone or in combination with other agents. Additionally, FDA approval for morphine and ziconotide is for monotherapy whereas combination therapy is often used in clinical practice. Combination therapy may prove to be superior to monotherapy given the complexity of pain signaling mechanisms; however, no human studies clearly attest to that potential. For instance, while neuraxial administration of a combination of local anesthetics and opioids is synergistic for pain relief in rats (111,112), such assertion could not be easily made in human studies and may involve a number of variables (73,102-104,110,113-117). A randomized double blind cross over study looking at the addition of bupivacaine to deliver 4, 6, or 8 mg/day to an intrathecal pump already delivering chronic morphine or hydromorphone found no added benefit for bupivacaine (110). On the other hand, a double blind study of 20 cancer pain patients who have failed conservative medical management found that the combination of intrathecal morphine and bupivacaine blunted the escalation of intrathecal morphine dosing significantly (104). Intrathecal boluses of bupivacaine have been reported to control breakthrough pain in cancer pain patients within 10-15 minutes of administration (114,118). Given the high lipid solubility of bupivacaine, catheter tip location is likely critical for its effectiveness in regional pain conditions (119). Of importance, the ability to treat breakthrough pain with intrathecal boluses through programmable pumps

(Patient Therapy Manager®, Medtronic) has provided patients with substantial potential for improved relief (21). This relief may be experienced almost instantaneously when bupivacaine is administered and the catheter tip overlies the nerve(s) involved in transmission of the pain signal (114,118); as bupivacaine works by blocking sodium channels predominantly on small nerve rootlets entering the spinal cord and less so by diffusing into the dorsal horn of the spinal cord (103). Whether the use of intrathecal bolus therapy increases efficacy of IDDS in managing chronic pain is unknown given the lack of such studies, especially in the setting of combination therapy, likely due to the above cited limitations.

Complications related to intrathecal therapy can be technical, biological, or medication related. While the vast majority of complications are minor, some serious complications can occur. An increased mortality rate in patients with non-cancer pain receiving intrathecal opioid therapy (mortality rate of 0.088% at 3 days after implantation, 0.39% at one-month, and 3.89% at one-year) was identified as likely related to the opioids as well as other factors that may be mitigated especially at the start of therapy (120,121). Other serious complications include granuloma formation that may be related to the amount and concentration of opiates, mostly morphine and hydromorphone (47,122-127). Surgical interventions in these cases are rare (128) as most cases improve with weaning off the intrathecal opiate, replacing it with preservative-free saline which has been shown to reverse the course leading to resolution of the granuloma (122,123). Granulomas may occur in as many as 3% of implanted patients and most are asymptomatic (129). Routine MRIs to rule out intrathecal granulomas was not recommended by the authors of this prospective study given the relatively low incidence (129). The earliest sign of granuloma may be increased pain despite increasing opiate infusion; hence, clinical vigilance is of prime importance. Other complications of IDDS include catheter kinking, catheter fracture/leakage, catheter migration, CSF leak, seroma, hygroma, infection, pump erosion through the skin, and medication side effects including but not limited to pruritus, nausea, vomiting, respiratory depression, and cognitive side effects.

The major limitation of this systematic review is the limited evidence for intrathecal infusion systems that is derived from randomized trials. Randomized trials provide valuable evidence about treatments and other interventions. However, most of the research and clinical practice comes from observational studies (130,131). Randomized trials work by first assuming there is no difference between a new and an old, or placebo treatment to prove the null hypothesis (132). Basically, it may be described that the standard RCTs are in fact set up to show that treatments do not work, rather than to demonstrate that treatments do work (132). Essentially the RCTs are designed to stop therapeutic bandwagons in their tracks and also practioners peddling worthless treatments to patients made vulnerable and desperate by their illness. However, most questions in medical research are investigated in observational studies (130,131,133-137). Consequently, observational studies are more likely to provide an indication of daily medical practice (138). Thus, the proponents of observational studies describe that observational studies are just as effective as RCTs. However, from a methodological perspective, the 2 types of studies are considered complementary rather than opposing (137). Thus, in clinical practice specifically involving interventions and surgery, observational studies and RCTs can be viewed as expressions in the setting of modern clinical research of the steps of observational and experimentation that form the basis of scientific methodology. Guyatt and Drummond (139) in a description of the hierarchy of strength of evidence for treatment decisions provide significant strength to systematic reviews of observational studies and single observational studies. Further disadvantages have been noted about the observational studies where research is often not detailed and clear enough to assess the strength and weaknesses of the investigations (130,131,140-158). However, in health technology assessment, Deeks et al (144) concluded that the results of observational studies sometimes, but not always, differ from results of randomized studies of the same intervention. Further, Hartz et al (159) in assessing observational studies of medical treatments, concluded that reporting was often inadequate to compare the study designs or allow other meaningful interpretation of results.

However, the concept that assignment of subjects randomly to either experimental or control groups as the perfect science has been questioned (160). While researchers believe that randomization ensures that participating groups will differ only by chance, it does not guarantee that the balance will actually be achieved through randomization (161-163). In fact, in a comparison of randomized and observational samples, there was only one significant difference when patients were allocated by means of non-randomization among

groups or compared to the total sample, in contrast to randomization showing significant difference in 7 parameters indicating that a randomized design may not be the best in interventional pain management settings (162). Further, issue of placebo is extremely crucial and quite difficult in interventional pain management settings with treatments such as intrathecal infusion systems given ethical and legal issues with currently only two agents being FDA approved and having only a single chamber intrathecal pump. In contrast, Benson and Hartz (164) in a 2000 publication comparing observational studies and RCTs, found little evidence that estimates of treatment effects in observational studies reported after 1984, were either consistently larger than or qualitatively different from those obtained in RCTs. Hartz et al (165), in assessing observational studies of chemonucleolysis, concluded that the results suggested that review of several comparable observational studies may help evaluate treatment, identify patient types most likely to benefit from a given treatment, and provide information about study features that improve the design of subsequent observational studies or even RCTs. However, they also cautioned that potential of comparative observational studies has not been realized because of concurrent inadequacies in their design, analysis, and reporting. Concato et al (166) in a 2000 publication evaluating published articles in 5 major medical journals from 1991 to 1995, concluded that the results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in RCTs on the same topic. Shrier et al (167) found that the advantages of including both observational studies and randomized trials in a meta-analysis could outweigh the disadvantages in many situations and that observational studies should not be excluded a priori. Thus, we believe that this review provides optimal evaluation including randomized and observational studies as well as evaluating for chronic cancer and non-cancer pain.

Given all the above and despite the potential for serious complications, intrathecal drug delivery remains a valuable therapy for chronic painful conditions, both cancer and non-cancer related. This therapy is often employed as a last resort in patients who have failed multiple other treatment modalities and has been shown to be effective when other interventions have failed. Significant challenges limit progress with intrathecal therapies. These may include the complex nature of pain and the frequent need to use a combination of drugs, many of which are not FDA approved for use in the intrathecal space. The current use of a single-chamber pump to deliver multiple medications poses particular dosing challenges when combination therapy is employed. Additionally, poor reimbursement for what is deemed a labor intensive task that requires high level vigilance from the managing physician is limiting the access of deserving patients to this important form of therapy (168). This factor may additionally limit the development of needed novel agents that would offer improved analgesia and would have a more favorable safety profile. It is hoped that this therapy will remain a viable option for effective pain relief for patients with refractory chronic pain and that technological and pharmacological developments will improve its safety and efficacy in the future.

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## Disclosures

**Author Contributions:** Dr. Hayek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Hayek, Deer, Pope and Patel designed the study protocol. Dr. Hayek managed the literature searches and summaries of previous related work and wrote the firsts draft of the manuscript. All other authors provided revision for intellectual content and final approval of the manuscript.

**Conflict of Interest:** All authors have no conflicts of interest to report relevant to intrathecal therapy. None of the authors of the manuscript received any remuneration for writing the manuscript. Further, the authors have not received any reimbursement or honorarium in any other manner. Deer is a consultant for Medtronic, Medasys, and Codman. The authors are not affiliated in any manner with manufacturers of pain pumps. However, all the authors are members of the American Society of Interventional Pain Physicians (ASIPP) and practicing interventional pain physicians.

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