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Systematic Review

Intrathecal Infusion Systems for Long-Term Management of Chronic Non-Cancer Pain: An Update of Assessment of Evidence

Frank J.E. Falco, MD[1], Vikram Patel, MD[2], Salim M. Hayek, MD, PhD[3], Timothy R. Deer, MD[4], Stephanie C. Geffert, MLIS[5], Jie Zhu, MD[6], Obi Onyewu, MD[7], Sareta Coubarous, DO[8], Howard S. Smith, MD[9], and Laxmaiah Manchikanti, MD[10]

From: [1,5-8]Mid Atlantic Spine & Pain Physicians, Newark, DE, and Temple University Hospital, Philadelphia, PA; [2]ACMI Pain Care, Algonquin, IL; [3]University Hospitals of Cleveland, Cleveland, OH, and a member of the Outcomes Research Consortium, Cleveland, OH; [4]Center for Pain Relief, Charleston, WV, and West Virginia University School of Medicine Charleston, WV; [9]Albany Medical College, Albany, NY; and [10]Pain Management Center of Paducah, Paducah, KY, and University of Louisville, Louisville, KY.

Additional author affiliations on P. SE 205

Address correspondence:
Laxmaiah Manchikanti, M.D.
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

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Dr. Hayek is a consultant for Boston Scientific.
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Dr. Deer is a consultant and research advisor for Bioness, Flowonix, Jazz, Medtronic, Nevro, St. Jude, Spinal Modulation, and Vertos.

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Background: Intrathecal infusion systems are often used for patients with intractable pain when all else fails, including surgery. There is, however, some concern as to the effectiveness and safety of this treatment.

Study Design: A systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain.

Objective: To evaluate and update the effect of intrathecal infusion systems in managing chronic non-cancer pain.

Methods: The available literature on intrathecal infusion systems in managing chronic pain was reviewed. The quality assessment and clinical relevance criteria utilized were the Cochrane Musculoskeletal Review Group criteria as utilized for interventional techniques for randomized trials and the Newcastle-Ottawa Scale criteria for observational studies. The level of evidence was classified as good, fair, and limited or poor based on the quality of evidence developed by the U.S. Preventative Services Task Force (USPSTF). Data sources included relevant literature identified through searches of PubMed and EMBASE from 1966 to December 2012, and manual searches of the bibliographies of known primary and review articles.

Outcome Measures: The primary outcome measure was pain relief with short-term relief < 12 months and long-term relief ≥ 12 months. Secondary outcome measures were improvement in functional status, psychological status, return to work, and reduction in opioid intake.

Results: There were 28 studies identified for this systematic review. Of these, 21 were excluded from further review. A total of 7 non-randomized studies met inclusion criteria for methodological quality assessment. No randomized trials met the inclusion requirements.

The evidence is limited based on observational studies.

Limitations: The limitations of this systematic review include the paucity of literature.

Conclusion: The evidence is limited for intrathecal infusion systems.

Key words: Spinal pain, chronic low back pain, intrathecal infusion, intrathecal infusion systems, intrathecal drug delivery systems, intrathecal pumps, chronic non-cancer pain, chronic non-malignant pain, morphine, bupivacaine, ziconotide

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Intrathecal infusion systems are most commonly used in the treatment of recalcitrant chronic cancer or non-malignant pain after all other methods have failed including conservative and surgical treatment. According to Turner et al (1), intrathecal opioid therapy via implantable drug delivery systems has been an option for the treatment of chronic pain since the early 1980s. The use of intrathecal pumps been criticized based on the American College of Occupational and Environmental Medicine (ACOEM) and American Pain Society (APS) guidelines that claim there is a lack of effectiveness (2-6). ACOEM guidelines have come under scrutiny due to their incomplete review of the literature with exclusion of recent high quality published studies, outdated assessment criteria, inconsistent conclusions, and failure to comply with current standards for producing high quality objective guidelines for various interventional techniques according to the Appraisal of Guidelines for Research and Evaluation (AGREE), American Medical Association (AMA), and Institute of Medicine (IOM) (7-12). Similarly, APS guidelines have been critically appraised (3-6,13-15).

Hayek et al (16) published a systematic review on intrathecal therapy for cancer and non-cancer pain in 2011 and concluded that 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. They also noted that the recommendation for intrathecal infusion systems is limited to a moderate recommendation for non-cancer pain based on the current moderate evidence derived from 15 observational studies for chronic non-cancer pain. They subsequently concluded that intrathecal drug delivery remains a valuable therapy for chronic painful conditions, both cancer and non-cancer related, and is often employed as a last resort.

In an updated published practice guidelines for chronic pain management (17) by the American Society of Anesthesiologists (ASA) Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine (ASRA), it was concluded that intrathecal injection or infusion for neuropathic pain can provide up to 12 months of pain relief. These guidelines recommended that intrathecal opioid injection or infusion may be used for patients with neuropathic pain.

Patel et al (18) published a systematic review on intrathecal infusion systems for long-term management of chronic non-cancer pain in 2009 and concluded that there was limited evidence for intrathecal infusion systems providing long-term pain relief in chronic non-cancer pain. Although the evidence was limited based on 4 observational studies, their recommendation was strong for the use of intrathecal infusion systems for the treatment of chronic non-cancer pain.

The increasing prevalence of chronic pain and explosion of diagnostic and therapeutic modalities have resulted in a disproportionate increase in health care expenditures, and continue to be a major health policy issue in the United States and across the globe (19-80). Furthermore, the extensive use of oral opioids for all types of pain continues to escalate, as do the negative, side effects, complications, and fatalities, the numbers of which exceed motor vehicle injuries in the United States (81-105). Consequently, various types of intrathecal infusion systems with opioids and other agents have been developed for the management of chronic intractable pain (105-113). Even then, there is a paucity of literature in reference to intrathecal infusion systems for the long-term management of chronic non-cancer pain and a lack of randomized trials. In an atmosphere where the availability and synthesis of new information are constants, systematic reviews must be updated frequently (114-116).

The primary objective of this systematic review is to determine the effectiveness of intrathecal infusion systems in providing long-term pain relief to those with chronic non-cancer pain. Other secondary objectives of this review are to assess the effect on functional status and adverse consequences associated with intrathecal infusion systems.

The present systematic review is an update of a previous systematic review performed in 2009 (18).

1.0 Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials and observational studies (19,117-126), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (127,128), Standards for Reporting Observational Studies (STROBE) (129), Cochrane guidelines (124,125,130), Chou and Huffman's guidelines (3), and quality of reporting of analysis (122).

1.1 Criteria for Considering Studies

1.1.1 Types of Studies

Randomized controlled trials
Non-randomized observational studies
Case reports and reviews for adverse effects

1.1.2 Types of Participants

Participants of interest were adults aged at least 18 years with chronic pain of at least 6 months duration. Patients must have failed previous pharmacotherapy, exercise therapy, and interventional techniques.

1.1.3 Types of Interventions

Programmable intrathecal infusion systems.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measures were functional improvement, change in psychological status, return to work, and the reduction or elimination of opioid use, other drugs, other interventions, and complications.
- At least 2 of the review authors independently, in an unblinded standardized manner, assessed the outcomes measures. Any disagreements between reviewers were resolved by a third author and/or consensus.

1.2 Literature Search

Searches were performed from the following sources:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
3. Previous systematic reviews and cross references
4. Clinical Trials: clinicaltrials.gov/

The search period includes articles from 1966 to December 2012.

1.3 Search Strategy

The search strategy emphasized chronic non-cancer pain with intrathecal infusion systems. At least 2 review authors independently, in an unblinded standardized manner, performed each search. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and/or consensus.

Search terms included: chronic pain, opioid infusions, and intrathecal infusion systems.

1.4 Data Collection and Analysis

The review focused on randomized trials, observational studies, and reports of complications. The population of interest was patients suffering with chronic pain of non-cancer origin. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports were excluded.

1.4.1 Selection of Studies

- Two review authors, in an unblinded standardized manner, screened the abstracts, of all identified studies against the inclusion criteria.
- The authors then retrieved all possibly relevant articles in full text for comprehensive assessment of internal validity, quality, and satisfaction of inclusion criteria.

1.4.2 Inclusion and Exclusion Criteria

1. Are the patients described in sufficient detail to allow you to decide whether they are comparable to those that are seen in clinical practices of interventional pain management?
   A. Setting – office, hospital, outpatient, inpatient
   B. Physician – interventional pain physician, general physician, anesthesiologist, physiatrist, neurologist, rheumatologist, orthopedic surgeon, neurosurgeon, etc.
   C. Patient characteristics - duration of pain
   D. Non-interventional techniques or surgical intervention in the past
2. Is the intervention described well enough to enable you to provide the same for patients in interventional pain management settings?
   A. Nature of intervention
   B. Frequency of intervention
   C. Duration of intervention
3. Were clinically relevant outcomes measured?
   A. Proportion of pain relief
   B. Disorder/specific disability
   C. Functional improvement
   D. Allocation of eligible and non-eligible patients to return to work
   E. Ability to work

1.4.3 Clinical Relevance

Clinical relevance of the included studies was evaluated according to 5 questions recommended by the Cochrane Back Review Group (124,130). Table 1 shows the clinical relevance questions. Each question will be scored positive (+) if the clinical relevance item was met, negative (–) if the item was not met, and unclear (?) if data were not available to answer the question.

1.4.4 Methodological Quality or Validity Assessment

The methodological qualities assessment was performed by 2 review authors who independently assessed, in an unblinded standardized manner, the in-

ternal validity of all the studies. The methodological quality assessment was performed in such a manner as to avoid any discrepancies. Any such discrepancies were evaluated by a third reviewer and settled by consensus. The quality of each individual article used in this analysis was assessed by the Cochrane review criteria (Table 2) (125) for randomized trials and the Newcastle-Ottawa Scale for observational studies (Tables 3 and 4)

Table 1. *Clinical relevance questions.*

Questions	P(+)	N(-)	U (unclear)
A) Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?			
B) Are the interventions and treatment settings described well enough so that you can provide the same for your patients?			
C) Were all clinically relevant outcomes measured and reported?			
D) Is the size of the effect clinically important?			
E) Are the likely treatment benefits worth the potential harms?			

Scoring adapted from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (130).

Table 2. *Randomized controlled trials quality rating system.*

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are: alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/ Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. Should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events determined by interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/ Unsure
D	Were incomplete outcome data adequately addressed?		
	6. Was the drop-out rate described and acceptable?	The number of participants included in the study but who did not complete the observation period or were not included in analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up, and does not lead to substantial bias a "yes" is scored. (N.B. %s arbitrary, not supported by literature).	Yes/No/ Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/ Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/ Unsure

Table 2 (cont.). ***Randomized controlled trials quality rating system.***

F	Other sources of potential bias:		
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/ Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/ Unsure
	11. Was compliance acceptable in all groups?	The reviewer determines if compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/ Unsure
	12. Was the outcome assessment timing similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Unsure

Adapted and Modified: Furlan AD, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (125).

Table 3. ***Newcastle-Ottawa quality assessment scale: Case control studies.***

Selection
1) Is the case definition adequate?
a) yes, with independent validation *
b) yes, e.g. record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated
3) Selection of Controls
a) community controls *
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint) *
b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Exposure
1) Ascertainment of exposure
a) secure record (eg surgical records) *
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes *
b) no
3) Non-Response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (131).

Table 4. *Newcastle-Ottawa quality assessment scale for cohort studies.*

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community
b) somewhat representative of the average _____ in the community *
c) selected group of users e.g. nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (eg surgical records) *
b) structured interview *
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes *
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability
Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (131).

(131). For nonrandomized observational studies, the patient population should have been at least 50 total or at least 25 in each group if they were comparison groups.

If there was a conflict of interest with the reviewed manuscript concerning authorship (if the reviewer was one of the authors) or any other type of conflict, the involved authors did not review the manuscript for quality assessment.

For adverse effects, confounding factors, etc., it was not possible to use quality assessment criteria. Thus, these were considered based on an interpreta-

tion of the reports published and critical analysis of the literature.

Only randomized trials meeting the inclusion criteria with at least 50% of applicable criteria were utilized for analysis. However, studies scoring less also would be described and provided with an opinion and critical analysis.

Observational studies have to meet a minimum of 50% of the applicable criteria for cohort studies and case-control studies. Studies scoring less would also be described and provided with an opinion and a critical analysis.

If the literature search provided at least 5 randomized trials meeting the inclusion criteria and they were homogenous for each modality and condition evaluated, a meta-analysis was performed.

1.4.5 Data Extraction and Management

Two review authors independently, in an unblinded standardized manner, extracted the data from the included studies. Disagreements were resolved by discussion between the 2 review authors; if no agreement was reached, a planned third author decided.

1.4.6 Measurement of Treatment Effect in Data Synthesis (Meta-Analysis)

Data were summarized using meta-analysis when at least 5 studies were available meeting the inclusion criteria. Qualitative (the direction of a treatment effect) and quantitative (the magnitude of a treatment effect) conclusions were evaluated. Random-effects meta-analysis to pool data was also used.

The minimum amount of change in pain score to be clinically meaningful has been described as a 2-point change on a scale of 0 to 10 (or 20 percentage points), based on commonly utilized findings in trials studying general chronic low back pain (120,122,124,132-135). However, recent descriptions of clinically meaningful improvement showed either pain relief or functional status as 50% (136-156). Consequently, for this analysis, we utilize clinically meaningful pain relief of at least a 3-point change on an 11-point scale of 0 to 10, or 50% pain relief from the baseline, as clinically significant and functional status improvement of 40% or more.

1.4.7 Integration of Heterogeneity

The evidence was assessed separately by administration to each condition. The meta-analysis was performed only if there were at least 5 studies meeting inclusion criteria available for each variable.

Statistical heterogeneity was explored using univariate meta-regression (155,156).

1.5 Summary Measures

Summary measures include 50% or more reduction of pain in at least 40% of the patients, or at least 3-point decrease in pain scores and relative risk of adverse events including side effects.

Short-term effectiveness was defined as improvement of less than 12 months; whereas, long-term effectiveness was defined 12 months or longer.

1.6 Analysis of Evidence

Analysis of evidence was performed based on United States Preventive Task Force (USPSTF) criteria as illustrated in Table 5, which has been utilized by multiple authors (157). Analysis will be conducted using 3 levels of evidence ranging from good, fair, and limited or poor. These criteria have been extensively utilized (3,158-174).

At least 2 of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there was

Table 5. *Method for grading the overall strength of the evidence for an intervention.*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least two consistent, high-quality RCTs or studies of diagnostic test accuracy).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice, or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; two or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least two consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited or poor	Evidence in sufficient to assess efforts on health outcomes because of limited number or power of studies, large and unexplained inconsistency between high-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Adapted from methods developed by U.S. Preventive Services Task Force (157).

a conflict with authorship, those authors were not involved in the assessment and analysis of the studies.

1.7 Outcome of the Studies

A randomized trial study was positive if the intrathecal infusion treatment for chronic nonmalignant pain was clinically relevant and effective in regards to pain relief compared to placebo or an active control. A randomized trial study was negative if there was no significant difference in pain relief between the treatment groups or no improvement from baseline. Outcomes were judged at distinct reference points with positive or negative results reported at 6 months, one year, and after one year.

An observational study was positive if the intrathecal infusion treatment for chronic nonmalignant pain demonstrated effective pain relief with outcomes reported at 6 months, one year, and later.

2.0 Results

Figure 1 shows a flow diagram of the study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (123).

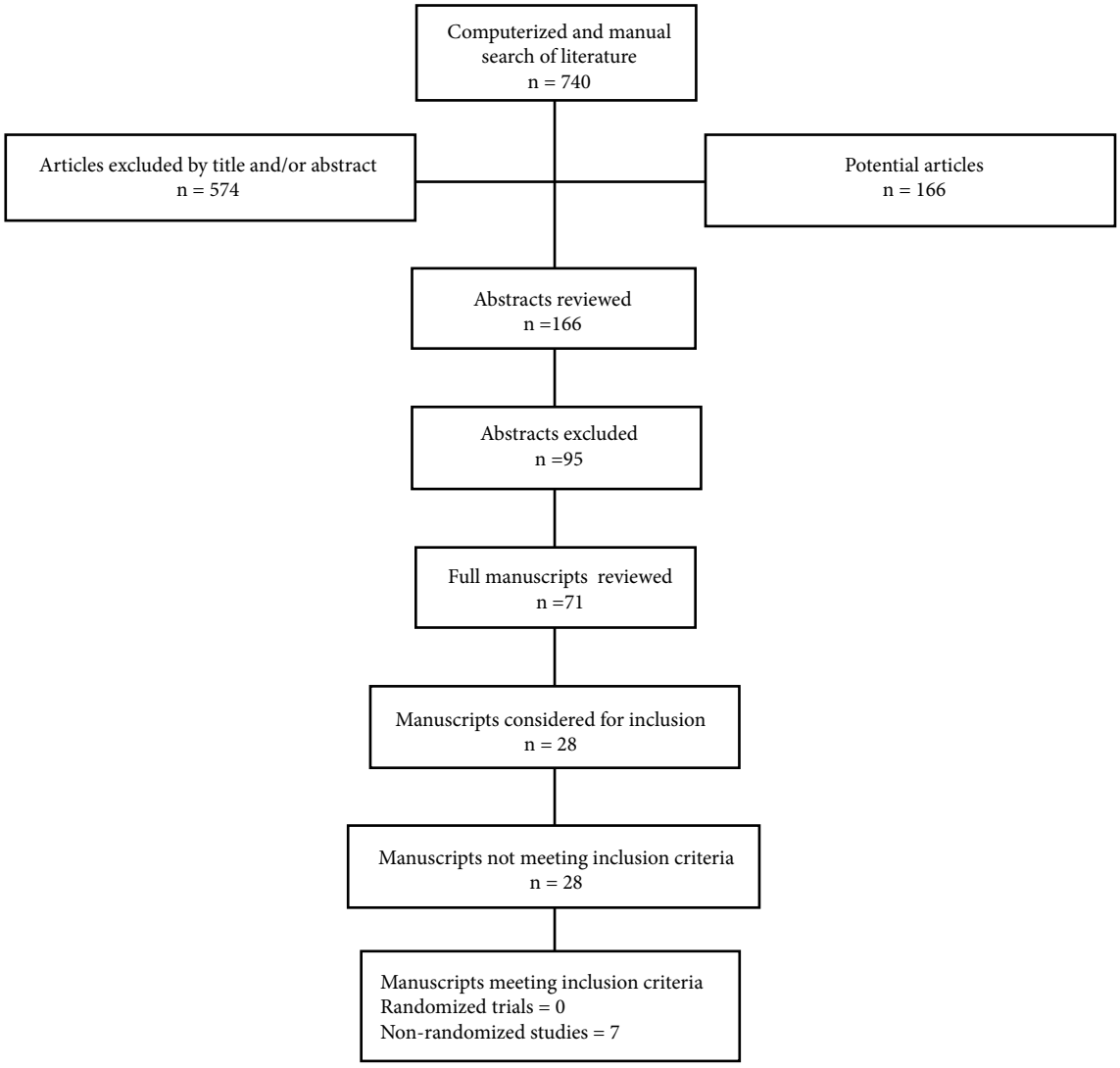

Fig. 1. *The flow diagram illustrating published literature evaluating the effectiveness of intrathecal infusion systems.*

Of 166 articles, there were 71 potential studies that resulted from the literature search and only 28 studies considered for inclusion (175-202). Table 6 lists the randomized trials and non-randomized studies that were excluded from this systematic study for not meeting the inclusion criteria.

There were 67 relevant studies that resulted from the literature search and only 28 studies considered for

Table 6. *List of excluded randomized trials and observational studies.*

Manuscript Author(s)	Condition Studied	# of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
Anderson et al, 2003 (175) Randomized trial	Chronic nonmalignant pain	37	3, 6 months	Small sample size
Burgher et al, 2007 (176) Retrospective cohort study	Infection control measures	92	N/A	Focus was on infection control measures not on relief of chronic pain.
Ooi et al, 2011 (177)	Chronic intractable pain and spasticity	166	4-51 months (mean=26 months)	Case series
Grider et al, 2008 (178)	Chronic pain	3	N/A	Case report
Hamann & Sloan, 2007 (179) Randomized, double-blind, prospective pilot study	Chronic pain	15	7 days	Small sample size
Hoelzer et al, 2010 (180)	Intractable abdominal pain	1	N/A	Case report
Knox et al, 2007 (181)	Intractable non surgical back pain	1	N/A	Case series
Langsam, 1999 (182)	Chronic low back pain	1	N/A	Case report
Lew et al, 2005 (183)	Spasticity	1	N/A	Case report
McMillan et al, 2003 (184) Cohort study	Chronic intractable pain	7	6, 12 months	Small sample size
Medel et al, 2010 (185)	Thoracic outlet syndrome	1	N/A	Case report
Murphy et al, 2006 (186)	Spasticity	1	N/A	Case report
Narouze et al, 2007 (187)	Spasticity	1	N/A	Case report
Rainov et al, 2001 (188) Pilot cohort study	Chronic back and leg pain	26	24 months	Pilot study and small patient sample size.
Shaladi et al, 2007 (189) Cohort study	Chronic pain secondary to vertebral compression fractures	24	12 moths	Small sample size
Smith et al, 2005 (190)	Chronic sickle cell pain	2	N/A	Case series
Teddy et al, 1992 (191) Retrospective cohort study	Intractable spasticity and various conditions such as traumatic spinal cord injury.	46	Not Clear	Smaller sample size, focus on complications not pain relief.
Tutak & Doleys, 1996 (192) Observational study	Chronic low back and leg pain of noncancer origin.	26	16-27 months (average=23 months)	Small sample size
Paice et al, 1996 (193) Retrospective, multicenter study	Chronic pain: Cancer and non cancer	429 usable patient forms with information about screening, outcomes, dosing and adverse effects.	N/A	Outcomes were about physician standard practices when using intraspinal opioids delivered via an implanted device, not on patient pain relief.
Atli et al, 2010 (194) Retrospective cohort study	Chronic non malignant pain	43	3 years	Small sample size
Hayek et al, 2011 (195) Retrospective cohort comparison study	Chronic non malignant pain	135	12 months	Excluded because the emphasis was on IT dose rate escalation between groups of younger and older patients.

N/A = Not applicable

inclusion (175-202). Of the 28 intrathecal infusion system studies identified, 21 were excluded (175-195). Ten articles were excluded because they were case studies/reports and case studies are not part of the inclusion criteria for this systematic review (177,178,180-183,185-187,190). Eight studies were excluded due to a small sample size with a study population of less than 50 (175,179,184,188,189,191,192,194). Three studies were excluded because the outcomes were not related to pain relief and did not meet the requirements for inclusion in this systematic review (176,193,195). Table 7 illustrates the characteristics of the 7 studies considered for inclusion (196-202).

Table 7. *Assessment of the non-randomized studies for inclusion criteria.*

Manuscript Author(s)	# of Patients	Methods	Follow-up Period	Outcome Measures
Deer et al, 2004 (196)	36 physicians enrolled 166 patients (90 males and 76 females) for drug-delivery systems trial. Success rate was 93% (154 patients). In all, 136 patients (82%) were implanted.	The National Outcomes Registry for Low Back Pain collected data at baseline, trialing, implant (or decision not to implant).	6 and 12 month follow-ups. Patients were asked to rate their quality of life and satisfaction with the therapy.	Numeric pain ratings and ODI ODI scores from implanted patients were compared among baseline and 6 and 12 month follow-ups.
Roberts et al, 2001 (197)	88 patients: 58 women and 30 men from 2 centers with chronic non-cancer pain.	All patients implanted with intrathecal DASs from 1989 to 1996 were identified. A self-administered questionnaire was posted to all patients.	Measured outcome in patients treated for at least 6 months.	Global pain relief and physical activity, medication consumption, work status, side-effects of intrathecal opioid administration, cessation of therapy, satisfaction with therapy, DAS-related complications, intrathecal drugs and doses after DAS implantation.
Thimineur et al, 2004 (198)	The study subjects included 38 PR while the comparative group included 31 intrathecal candidates who had an unsuccessful trial or declined intrathecal therapy, and another group of 41 newly referred patients. No gender data.	PR subjects were implanted with an intrathecal catheter and a constant flow or programmable pump.	Treatment and control groups completed questionnaires at entry (baseline) and 6 month intervals for 3 years until termination (36 months). Newly registered patients completed it only at initial evaluation and at 36 months.	Questionnaire packets included: SCL-90-R, SF-36, BDI, MPQ, ODI, pain drawing, and pain rating. Information was grouped into 3 groups.
Winkelmüller and Winkelmüller, 1996 (199)	162 patients identified but only 120 patients could be located: 60 males and 60 females. Data from original intrathecal drug therapy in the 120 patients and in continuing therapy of 82 patients.	Retrospective data collected from patients who received an infusion pump for continuous intrathecal opioid therapy for chronic nonmalignant pain between July 1988 and Nov. 1993.	The follow-up period for the study ranged from 6 months to 5.7 years. A first clinical evaluation was made 6 months after pump implantation.	A pain diary was kept, pain intensity was recorded 3 times daily according to VAS. Level of activity, patients' mood, and quality of life were also evaluated.
Rauck et al, 2010 (200)	110 patients. 11 patients withdrew from the study. No gender data.	Prospective 6 month cohort study of patients implanted with an intrathecal pump that delivered morphine for chronic intractable pain.	Monthly up to 6 months post intrathecal pump implantation.	Primary objective: to determine accuracy of drug delivery, measured as the ratio of drug delivered to drug programmed volume (DP ratio). VAS, NRS ODI, adverse events, and device-related complications also collected.
Veizi et al, 2011 (201)	126 consecutive non cancer intractable pain patients. 72 males and 54 females. Data collected in all 126 patients.	Retrospective study of implanted IDDSs and initiated with an intrathecal opioid as a single medication or an intrathecal opioid and bupivacaine.	3, 6, and 12 months postimplant.	Pain scores/VAS, oral opioids intake, IT opioid dose, IT medications type and rate, pain intensity scores.
Hamza et al, 2012 (202)	58 consecutive chronic non cancer pain patients. 33 males and 35 females. Data collected in all 58 patients.	Prospective cohort study of implanted IDDSs with low dose IT opioids.	6, 12, 18, 24, and 36 months postimplant	Pain scores, oral opioids intake, IT opioid dose, BPI (Worst and Average pain), BPI (Physical Functioning), BPI (Behavior), BPI (Enjoyment), PGA (Patient Reported Pain and Functional Improvement).

ODI = Oswestry Disability Index; DASs = Drug Administration Systems; IDDSs = Intrathecal drug delivery systems; PR = Pump recipients; SCL-90-R = Symptom checklist 90-R; SF-36 = Short-form 36; BDI = Beck Depression Inventory ; MPQ = McGill Pain Questionnaire ; VAS = Visual Analog Scale; NRS = Numerical Rating Scale; BPI = Brief Pain Inventory; PBG = Patient Global Assessment

2.1 Clinical Relevance

Of the 7 studies assessed for clinical relevance, all studies met the criteria with a score of 4 of 5 or greater (196-202). Table 8 illustrates an assessment of clinical relevance.

2.2 Methodological Quality Assessment

A methodological quality assessment of the non-randomized observational studies meeting inclusion criteria was carried out utilizing the Newcastle-Ottawa Scale as illustrated in Table 9. For cohort studies, stud-

Table 8. *Clinical relevance of included studies.*

Manuscript Author(s)	A) Patient description	B) Description of interventions and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E) Benefits vs. potential harms	Total Criteria Met
Deer et al (196)	+	_	+	+	+	4/5
Roberts et al (197)	+	+	+	+	+	5/5
Thimineur et al (198)	+	+	+	+	+	5/5
Winkelmüller and Winkelmüller (199)	_	+	+	+	+	4/5
Rauck et al (200)	+	+	+	+	+	5/5
Veizi et al (201)	+	+	+	+	+	5/5
Hamza et al (202)	+	+	+	+	+	5/5

+ = positive; - = negative; U = unclear
Scoring adapted from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (130).

Table 9. *Methodological quality assessment of cohort studies of intrathecal infusion systems utilizing Newcastle-Ottawa quality assessment scale.*

	Deer et al (196)	Roberts et al (197)	Thimineur et al (198)	Winkelmüller and Winkelmüller (199)	Rauck et al (200)	Veizi et al (201)	Hamza et al (202)
Selection							
1) Representativeness of the exposed cohort							
a) truly representative of the average chronic non-cancer pain patient in the community*	X	X	X	X	X	X	X
b) Somewhat representative of the average chronic non-cancer pain patient in the community*							
c) Selected group of users e.g. nurses, volunteers							
d) no description of the derivation of the cohort							
2) Selection of the non exposed cohort							
a) drawn from the same community as the exposed cohort*	X	X	X	X	X	X	X
b) drawn from a different source							
c) no description of the derivation of the non exposed cohort							
3) Ascertainment of exposure							
a) secure record (eg surgical records) *						X	
b) structured interview*	X	X	X		X		X
c) written self report				X			
d) no description							
4) Demonstration that outcome of interest was not present at start of study							
a) yes*	X	X	X	X	X	X	X
b) no							

Table 9 (cont.). *Methodological quality assessment of cohort studies of intrathecal infusion systems utilizing Newcastle-Ottawa quality assessment scale.*

	Deer et al (196)	Roberts et al (197)	Thimineur et al (198)	Winkelmüller and Winkelmüller (199)	Rauck et al (200)	Veizi et al (201)	Hamza et al (202)
Comparability							
1) Comparability of cohorts on the basis of the design or analysis							
a) study controls for duration of pain. *	X	X	X	X	X	X	X
b) study controls gender.*							
Outcome							
1) Assessment of outcome							
a) independent blind assessment *							
b) record linkage *	X	X	X	X	X	X	X
c) self report							
d) no description							
2) Was follow-up long enough for outcomes to occur							
a) yes (select an adequate follow up period for outcome of interest)	X	X	X	X	X	X	X
b) no							
3) Adequacy of follow up of cohorts							
a) complete follow up- all subjects accounted for *						X	X
b) subjects lost to follow up unlikely to introduce bias-small number lost < 30 %*	X	X	X	X	X		
c) follow up rate < 50% and no description of those lost							
d) no statement							
Total:	8/12	8/12	8/12	8/12	8/12	8/12	8/12

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.
Adapted and modified from: Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (131).

ies scoring 67% or higher were considered high quality, studies scoring 50% or higher were considered moderate quality, and studies scoring less than 50% were considered low quality and were excluded. There were 7 non-randomized cohort studies that met the criteria for high methodological quality.

For case-control studies, 67% or higher was considered as high quality and, 50% or higher was considered as moderate quality, and less than 50% was considered low quality. All low quality studies were excluded. There were no case-control studies that met the inclusion criteria.

Randomized control trials were assessed by the Cochrane review criteria. No randomized studies met inclusion criteria for this systematic review.

2.3 Meta-Analysis

No meta-analysis was performed because there were no randomized trials that met the inclusion criteria.

2.4 Study Characteristics

Table 10 illustrates the study characteristics of the included studies for observational studies evaluating intrathecal infusion systems.

2.5 Analysis of Evidence

Overall, the 7 studies evaluating intrathecal infusion systems demonstrated pain relief and improvement in function. There were 6 studies that showed positive results for long-term pain relief (196-199,201,202) at ≥

Table 10. *Characteristics of included studies of intrathecal infusion systems*

Reference, Year	Participants	Interventions	Outcomes	Results	Conclusions
Deer et al, 2004 (196)	36 physicians enrolled 166 patients who were trialed for IT drug-delivery system. 154 patients had a successful trial and 136 were implanted.	136 patients received IT pump implantation after successful trial and were followed for 12 months. Pain and function were evaluated during the study as well as use of systemic opioids, return to work, patient satisfaction and adverse events.	Numeric pain ratings and ODI scores at baseline, 6 months, and 12 months.	The trialing success rate was 93% (154 patients). 136 (82%) were implanted. At 12-month follow-ups, 80% of implanted patients were satisfied with their therapy and 87% said they would undergo the procedure again.	Study concluded that IDDSs were successful in managing chronic low back pain. QOL improvements were significant, vast majority of IDDS patients (80%) satisfied with their therapy. Additional studies may help to better determine predictors for successful trials and quantify the benefits of IDDS for managing chronic low back pain.
Roberts et al, 2001 (197)	88 patients (58 women and 30 men). Mean age 53.4 years with non-cancer pain present on average for 9.8 years. 67 patients completed the questionnaires.	Patients were evaluated following treatment with intrathecal opioids for an average duration of 36.2 months. Patients had to be treated for more than 6 months with intrathecal opioids administered via totally implanted drug administration systems at 2 centers.	Duration of pain, pain treatments prior to intrathecal opioid administration, work status prior to therapy, technical complications, side effects, Global Pain Relief, 4 day medication diary	A majority of patients reported an increase in activity levels following intrathecal opioid therapy. There was no significant change in work status. There was a significant reduction in medication consumption after intrathecal opioid therapy. Some side effects/adverse events were reported.	This study demonstrated improvement in analgesia and self-reported activity levels, a reduction in medication intake and high levels of patient satisfaction with long-term intrathecal opioid administration via implanted drug administration devices. Recommend that further prospective studies determine the precise role and effectiveness of intrathecal opioid therapy.
Thimineur et al, 2004 (198)	38 intrathecal pump recipients and 31 IT candidates who had an unsuccessful trial or declined the IT therapy completed the study of the 88 enrolled, and another comparison group of 41 newly referred patients.	The study was a prospective evaluation of IT opioid treatment for chronic non-malignant pain. PR and non-recipients completed identical questionnaire packets. Newly registered patients completed the same questionnaires only twice.	1. Pain-SCL-90R, VAS, pain drawing, McGill. 2. Physical function SF-36, physical function subscale, ODI. 3. Mood-SCL-90R, depression and anxiety subscales, BDI	Intrathecal treatment had a significant impact on pain, function, and mood among study patients. The average reductions in pain in this study were less impressive than previous studies.	This study concluded that IT opioid therapy for non-malignant pain should be considered appropriate only when all conservative medical management has been exhausted.
Winkelmüller and Winkelmüller, 1996 (199)	162 patients with an infusion pump for continuous intrathecal opioid therapy for chronic nonmalignant pain were identified from the retrospective but they were only able to locate 120 patients for the study.	A retrospective investigation that focused on data available for 120 patients, could not locate data for the other 42 patients. The follow-up period for the study ranged from 6 months to 5.7 years. Of the 120 patients examined in the follow-up period, 82 patients still received intrathecal opioid therapy with a functioning implant.	VAS, dosage history, level of activity, patient mood and quality of life	The most unpleasant side effects described by the patients were increased sweating (8.5%) and a tendency to form peripheral edemas (6.1%). Good results were achieved in 74.2% of patients, and a reduction of pain in approximately 60% was reported. 92% of patients accepted the therapy and 81% reported a significant improvement in their quality of life.	The results of this retrospective study have to be cautiously viewed as far as a "life-time" treatment is concerned. Further investigations in a prospective study design are needed.
Rauck et al, 2010 (200)	110 patients were enrolled and implanted with an IT pump for the treatment of chronic intractable nonmalignant and cancer pain with an infusion of morphine. All but 3 cancer patients had chronic non-malignant pain.	A prospective observational study to evaluate the accuracy and efficacy of IT morphine administration using a new programmable pump. Follow-up was monthly up to 6 months. 11 patients withdrew from the study due to implant site infection, wound dehiscence, consent refusal, implant site pain, and MRI to rule out granuloma.	VAS, NRS, ODI, adverse events, device-related complications	The primary objective was to determine accuracy of drug delivery, measured as the ratio of drug delivered to drug programmed volume (DP ratio). The mean accuracy was 97.1% with a 90% confidence interval of 96.2 - 98.0%. Secondary objectives of efficacy demonstrated statistically significant reduction in mean pain and disability scores at each month. There were no serious adverse events (SAEs) or device related complications.	The new IT pump was shown to accurately deliver the programmed volume of IT morphine. In addition there was a significant improvement in pain relief and function. There were no serious adverse effects or device related complications.

Table 10 (cont.). *Characteristics of included studies of intrathecal infusion systems*

Reference, Year	Participants	Interventions	Outcomes	Results	Conclusions
Veizi et al, 2011 (201)	126 consecutive non-cancer intractable pain patients implanted with IT drug delivery system and initiated with an IT opioid as a single medication or an IT opioid and bupivacaine	A retrospective study to examine the effect of IT coadministration of bupivacaine with opioids during the initial phase of opioid titration and up to 1 year after implantation of an IT drug delivery system (IDDS).	Pain relief, oral opioid consumption, IT opioid, and bupivacaine dosage.	Significant reduction in pain intensity was found in both groups at 12 months post-implant. No major adverse effects were reported in this study.	Concomitant initial coadministration of IT bupivacaine with opioids blunts the rate of IT opioid dose escalation during the first year after implant of an IDDS. More studies are recommended.
Hamza et al 2012 (202)	61 consecutive non-cancer intractable pain patients underwent an IT trial of opioids. 3 patients failed the trial. 58 implanted with IT pump.	A prospective study to evaluate IDDS with low dose IT opioids. Follow up at 6, 12, 18, 24, and 36 months.	Pain scores, oral opioids intake, IT opioid dose, BPI (Physical Functioning, Behavior, Enjoyment), and (Behavior), PGA (Pain and Functional Improvement)	Significant pain relief, improved function, behavior, and enjoyment. IT dose minimal increase with average of 11.4% over 36 months. Significant decrease in oral opioid use.	Study demonstrated significant pain relief, reduction in oral opioids, and functional improvement from low dose IT opioid therapy with a nominal increase in the IT dose over a 3 year period.

IT = Intrathecal; IDDS = Intrathecal drug delivery systems; ODI = Oswestry Disability Index; QOL = Quality of life; PR = Pump recipients; SCL-90-R = Symptom checklist 90-R; VAS = Visual Analog Scale; SF-36 = Short-form 36; BDI = Beck Depression Inventory; MPQ = McGill Pain Questionnaire; NRS = Numerical rating scale; BPI = Brief Pain Inventory; PBG = Patient Global Assessment

12 months. There were 3 studies that showed positive results for short-term relief (200-202) at ≤ 12 months. There was significant improvement in function demonstrated in 5 of the 7 studies both short-term ≤ 12 months (196,197,199,200,202) and long-term at ≥ 12 months (196-199,202). Table 11 illustrates results of the effectiveness of intrathecal opioid infusion therapy for the treatment of chronic nonmalignant pain.

2.6 Level of Evidence

Based on the USPSTF criteria, the evidence is considered at 3 levels – good, fair, and limited or poor. The indicated evidence for intrathecal opioid infusion therapy is limited for short-term and long-term pain relief and functional improvement in the treatment of chronic nonmalignant pain.

3.0 Complications

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 (203-239). 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 (237,238). Other serious complications include granuloma formation that may be related to the amount and concentration of opiates, mostly morphine and hydromorphone (239-245). Surgical interventions in these cases are rare (246) as most cases improve with weaning off of the intrathecal opiate, replacing it with preservative-free saline, which has been shown to reverse the course leading to resolution of the granuloma (240,241). Granulomas may occur in as many as 3% of implanted patients and most are asymptomatic (247). Routine MRIs to rule out intrathecal granulomas was not recommended by the authors of this prospective study given the relatively low incidence (247). 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, cerebrospinal fluid (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.

4.0 Discussion

This systematic review provides limited evidence for the effectiveness of intrathecal infusion systems in managing chronic non-cancer pain. The evidence is assessed for intrathecal opioid infusion systems in providing significant pain relief and functional improvement both short-term and long-term for chronic nonmalignant pain. The results of this systematic review are con-

Table 11. *Effectiveness of intrathecal infusion systems.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function		Short Term Relief < 12 mos.	Long Term Relief ≥ 12 mos.
					< 12 mos.	≥ 12 mos.		
Deer et al (196)	O	8/12	166 patients	Trialed for drug-delivery systems	↓Pain ↑Function	↓ Pain ↑ Function	N/A	P
Roberts et al (197)	O	8/12	88 patients	Intrathecal opioids administered via totally implanted drug administration systems at 2 centers	↓ Pain ↑Function	↓ Pain ↑ Function	N/A	P
Thimineur et al (198)	O	8/12	38 intrathecal pump recipients and 31 intrathecal candidates who had an unsuccessful trial or declined the IT therapy, and another group of 41 patients that were newly referred.	Prospective evaluation of IT opioid treatment for chronic non-malignant pain	N/A	↓ Pain ↑ Function	N/A	P
Winkelmüller and Winkelmüller (199)	O	8/12	120 patients	Retrospective study, infusion pump for continuous intrathecal opioid therapy for chronic nonmalignant pain	↓ Pain ↑Function	↓ Pain ↑ Function	N/A	P
Rauck et al (200)	O	8/12	110 patients	A prospective observational study to evaluate the accuracy and efficacy of IT morphine administration pump for the treatment of chronic intractable nonmalignant and cancer pain.	↓ Pain ↑Function	N/A	P	N/A
Veizi et al (201)	O	8/12	126 patients	Retrospective study, coadministration of bupivacaine with opioids during the initial phase of opioid titration and up to one year after implantation of an IT drug delivery system (IDDS)	↓ Pain	↓ Pain	P	N/A
Hamza et al (202)	O	8/12	58 patients	Prospective study of IDDS with low dose IT opioids for the treatment of chronic noncancer pain over a period of 3 years.	↓ Pain ↑Function	↓ Pain ↑ Function	P	P

O = Observational; IT = intrathecal; P=positive; N=negative; N/A = not applicable

sistent with the findings from the systematic review of Hayek et al (16) and Patel et al (18) along with the recommendations of the ASA Task Force on Chronic Pain Management and the ASRA (17).

ACOEM practice guidelines for the treatment of low back pain and the APS guidelines for the evaluation and management of low back pain (2-6) were unable to provide any clear rationale for conclusions that did not recommend IDDSs for treatment of most chronic nonmalignant pain conditions on the basis of insufficient evidence. In their rationale against recommending IDDSs, however, they note that there may be an indication for those who have failed multiple trials of different oral medications and other treatments and have undergone independent psychological consultation including psychometric testing that does not reveal a contraindication to implantation.

Both the ACOEM and APS guidelines are poorly organized, lack a systematic approach to evaluating the literature, use assessment tools that are not considered

standard, present their analysis in a disorganized fashion, are devoid of input from pain medicine physicians, make conclusions that are often inconsistent and based on an incomplete review of the literature, and/or rely on outdated research while ignoring more recent high quality published studies.

In 2004, Deer et al (196) obtained data on patient demographics, clinical practices, and long-term outcomes for patients with chronic low back pain treated with implantable drug-delivery systems. There were 36 physicians that enrolled 166 patients to be trialed for drug-delivery systems. There were 154 of the 166 patients that had successful trials and 136 of the successfully trialed patients went on to pump implantation. The data were prospectively collected at baseline, trial, 6 months, and at 12 months. The data gathered at baseline and at the trial included information such as age and gender, underlying cause of pain and previous pain treatments, work status, trialing site, and trial methodology. At 6 and 12 month follow-ups, data were collected on therapy outcomes, use of concomitant therapies, and patient work status. The IDDS group experienced a statistically significant reduction of numeric pain ratings when ratings were compared between baseline and 6 months and between baseline and 12 months. The numeric pain rating was reduced by more than 48% for back pain and 32% for leg pain at 12 months. At baseline, nearly 30% of the IDDS group had an Oswestry Disability Index (ODI) in the minimal to moderate disability range and 60% were in the severe disability range. By the 6 month follow-up, there were 65% in the minimal to moderate disability range. At the 12 month follow up, 73% were in the minimal to moderate disability range. Those in the severe disability range decreased to 30% and 22% respectively at the 6 and 12 month follow-up. At 12 months, 42% of the IDDS patients had reduced their use of oral opioids. At the 12 month follow-up, 87% of the IDDS group stated a fair to excellent quality of life (QOL), 80% were satisfied with the IDDS, 87% would repeat the implant, and 87% would recommend IDDS to a friend or family member. Adverse events were reported in 23 patients receiving an IDDS implant and 21 required surgery to correct the problem. Adverse events included infection, dislodgment/migration, and CSF leak. The most common adverse event was a reaction to the medication. Other reported events that were infrequent included catheter kinking and fractures. This study found that IDDSs are successful in managing chronic low back pain in patients who have not found effective relief with other therapies.

In Roberts et al study (197), 88 patients with chronic non-cancer pain present on average for 9.8 years were evaluated following treatment with intrathecal opioids for an average duration of 36.2 ± 2 months and a maximum of 4 years. All patients who had been treated with intrathecal opioids by implanted drug administration systems for at least 6 months were included and evaluated by a self-administered questionnaire. Information collected included pain duration, pain treatments prior to IDDS, work status, medication consumption, technical complications, and side effects of therapy. The mean global pain relief was 60% and 74% of patients reported an increase in activity levels post IDDS implant. Opioid consumption as measured by the Medication Quantification Scale (MQS) was 31.2 ± 2.6 prior to IDDS and 12.7 ± 1.4 ($P < 0.0001$). There was no change in work status ($P = 0.9999$). The mean intrathecal morphine dose increased from 9.95±1.49 mg/day at 6 months to 15.26 ± 2.52 mg/day at 36 months after initiation of therapy, suggesting that intrathecal opioid therapy is not significantly affected by the development of tolerance.

Side effects associated with opioids during IDDS were excessive sweating; weight gain; decreased concentration, cognition, or memory; nausea and vomiting; arthralgias; peripheral edema; pruritus; decreased libido; erectile dysfunction; and menstrual abnormalities. The most frequent complications found in this study were catheter dislodgement, occlusion, and nerve root irritation that resolved after catheter repositioning. Other complications included pump reposition due to pressure on the lower ribs and device rotation, pump removal and replacement due to malfunction, pump leakage, pocket hematoma, and wound infection. Pumps were permanently removed in 5 patients due to ineffective analgesia in 3 patients and neurological events in 2 patients -- a foot drop from an epidural hematoma after a catheter revision and an incidental brainstem cerebrovascular accident. Overall, 88% of the patients were satisfied with their IDDS. In conclusion, this study demonstrated improvement in analgesia and self-reported activity levels, a reduction in medication intake, and high levels of patient satisfaction with long-term intrathecal opioid administration via the IDDS.

Thimineur et al (198), in a prospective evaluation of the long-term outcome of intrathecal opioid therapy in chronic non-malignant pain, included 2 comparative groups. The study included 38 pump recipients, 2 comparative groups consisting of 31 intrathecal candidates and 41 newly referred patients. Pump recipient sub-

jects (PR) were those patients who had a successful trial and later received an implant. A non-recipient control group consisted of those patients who either underwent an unsuccessful trial (< 50% pain relief, or intolerable side effects) and/or for other reasons elected not to pursue intrathecal treatment. A second comparative group included a new patient (NP) group encompassing newly referred patients over a 4-month time period.

The PR and NP patients completed identical questionnaire packets at baseline and at 6 month intervals up to 36 months. The NP group completed the same questionnaire twice, once at baseline and at 36 months. The following data were collected and analyzed at baseline and at 6 month intervals over a 3-year period, and included the Symptom Checklist 90 (SLC-90), SF-36 Health Survey (SF-36), Beck Depression Inventory (BDI), McGill Pain Questionnaire (MPQ) (short form), ODI, pain drawings and pain rating on Visual Analog Scale (VAS), and morphine equivalent opioid intake. The data from the questionnaires were categorized into pain, function, and mood groups. During the study all subjects received other pain therapies as per the standard of care in the practice. This included the provision of oral and transdermal medications, psychological counseling and behavioral treatments, therapeutic injections (trigger points, spinal injections, nerve blocks), and physical therapy.

A total of 88 pump candidates enrolled into the study. Of these, 69 completed the study at 36 months with 38 in the PR group and 31 in the non-recipient group. 59 new patients enrolled in the other comparative group with 41 completing the study at 36 months. The mean baseline scores on all pain measures (VAS, SCL-90R [SOM], Pain Drawing, McGill) were significantly lower in the NP group ($P < 0.0000$, 0.001, 0.002, and 0.002 respectively) compared to PR and NR groups. At 36 months the NP group (SCL-90R somatization scale, VAS, Pain Drawing, McGill) significantly improved in all 4 pain measures ($P < 0.000001$, 0.000001, 0.001, 0.0001) and the PR group (SCL-90R somatization scale, VAS, McGill) significantly improved in 3 of 4 pain measures ($P < 0.0001$, 0.000001, 0.01) at 36 months. The NR scores had significantly worsened at 36 months.

The NP group did better than the PR and NR groups in regard to significant improvement in regards to function on the SF-36 ($P < 0.000001$) and the ODI ($P < 0.000001$) at 36 months. The PR group also showed functional improvement on the ODI ($P < 0.01$), but not on the SF-36. The NR group showed decreased functioning at 36 months.

The NP group mood scores were significantly better than the PR and NR groups on all measures (SCL-90 anxiety scale, SCL-90 depression scale, BDI) at baseline. The NP ($P < 0.000001$, 0.000001, 0.000001) and PR ($P < 0.001$, 0.001, 0.01) groups showed significant improvement on these measures while the NR group scores were significantly worse.

The average daily oral morphine and transdermal fentanyl use for PR group was significantly greater than the NR ($P < 0.002$, $P < 0.003$) and NP ($P < 0.0000$, $P < 0.002$) groups at baseline. The average daily oral morphine dose had significantly decreased for the PR group ($P < 0.0000$) and increased for the NR group ($P < 0.0000$) and the NP group ($P < 0.005$). At 36 months, the average hourly transdermal fentanyl dose had significantly decreased in the PR group, but increased in the NR group. The NP group also decreased but not to a significant degree.

Adverse events reported included pump pocket infections in 2 patients and kinking of the catheter in one patient requiring a revision. One patient experienced a transverse myelitis necessitating removal of the system and high dose steroids. Side effects included sedation, nausea, edema, and hypogonadism -- no patient required treatment and no one opted to discontinue the IDDS therapy.

This study concluded that intrathecal treatment had a significant impact on pain, function, and mood. The NP and PR groups had similar improvements in all 3 areas despite markedly different baselines and differences in opioid therapy. Patients with greater chronic pain as seen in the PR and NR groups require higher doses than those with less severity as seen in the NP group and tend to respond positively to them. Despite the improvement in the PR group, they ended up less functional and with more self-rated pain and mood disturbances at 3 years compared to the NP group. The NR group deteriorated despite the escalation of oral opioids and provision of injection treatments. Intrathecal opioid therapy for non-malignant pain should be considered appropriate only when all other conservative medical management has been exhausted.

The purpose of Winkelmüller's and Winkelmüller's study (199) was to examine, in a retrospective manner, the questions of dependency, tolerance, side effects, and long-term effects in a large number of patients subjected to this treatment. A total of 162 patients were provided with an infusion pump for continuous intrathecal opioid therapy for chronic nonmalignant pain. The retrospective study included 120 of those pa-

tients as 42 records could not be located. The follow-up period of this study ranged from 6 months to 5.7 years with a mean of 3.4 years ± 1.3. The patients were divided into 4 groups for comparison based on their underlying pathophysiology that included nociceptive, neuropathic, mixed nociceptive-neuropathic, and deafferentation pain. Data collected included VAS (0 = no pain to 100 = unbearable pain), activity level, mood, and subjective assessment of QOL. There was an evaluation at baseline prior to pump implantation, a first follow-up at 6 months post pump implantation, and at a last follow-up after pump implantation. There were 82 patients for whom data were collected at baseline, the first follow-up, and the last follow-up. By group there were 10 nociceptive, 5 neuropathic, 49 mixed nociceptive-neuropathic, and 18 deafferentation patients.

The average VAS at baseline, first follow-up and last follow-up for all groups combined was 93.6, 30.5, and 39.2 respectively. The nociceptive group had an average VAS of 94 (baseline), 22.2 (first follow-up), and 48.4 (last follow-up). The neuropathic group had an average VAS of 97.2 (baseline), 35 (first follow-up), and 37 (last follow-up). The mixed group had an average VAS of 92.7 (baseline), 32.9 (first follow-up), and 40.7 (last follow-up). The deafferentation group had an average VAS of 94.8 (baseline), 27.6 (first follow-up), and 30.3 (last follow-up). The neuropathic and deafferentation groups had the lowest average VAS scores at the last follow-up although there was no statistical difference between these 2 groups and the mixed group. The nociceptive group had the least reduction in VAS of the 4 groups.

In regards to activity, 94% of all the patients were passive or socially withdrawn due to the intense pain at the baseline evaluation. There was a significant improvement in activity at the last follow-up evaluation with only 43% of the patients ($P < 0.001$) classified as either passive or socially withdrawn. Mood also improved significantly at the last follow-up evaluation with 33% of patients reporting despair and depression compared to 88% at the baseline evaluation ($P < 0.001$). QOL was improved in 81% of patients at the last follow-up with 92% satisfied with their intrathecal pump therapy. During the intrathecal treatment 30 of the 82 patients did not take any additional medications. Mild sedatives were used occasionally by 14 patients and 12 patients used mild analgesics. Nine patients used strong sedatives and 17 patients used strong analgesics occasionally. There was no statistical correlation between pain and the use of additional medications.

Adverse effects required the replacement of 14 pumps due to skin perforations, irregular flow rates, refilling issues with a pump that had a single diaphragm for drug and bolus chambers, and an infection near a pump pocket. There were 25 surgical revisions for catheter disconnections or dislocations. Of the 120 patients, 25 pumps were explanted due to side effects from the intrathecal opioid (6), dural leak (5), opioid tolerance (3), addictive behavior (4), illness unrelated to the pump therapy (3), infection near pump pocket (1), lack of response to the intrathecal therapy (1), and unknown (2). Short-term side effects included constipation, disturbed micturition, nausea, vomiting, and pruritus at the beginning of therapy. Potency problems, loss of libido, and amenorrhea occurred for a period of 6 to 8 months after the beginning of treatment in some cases. Long-lasting side effects from intrathecal therapy included sweating and edema formation.

The authors concluded that the long-term use of intrathecal opioid therapy for nonmalignant pain should be used in carefully selected patients based on the results of their study. Intrathecal therapy was successful in providing good results in 74.2% of the patients in this study. They noted that pain was reduced by approximately 60% over the long-term and there was significant improvement in activity, mood, and QOL.

Rauck et al (200) evaluated 110 patients in a prospective, non-randomized, open-label, multi-center (7 sites) investigational device exemption study approved by the Food and Drug Administration (FDA) for the Prometra® IDDS. Patients were assessed monthly for up to 6 months. The patients consisted of those with cancer pain requiring strong opioids, chronic nonmalignant pain with a numeric rating scale (NRS) score ≥ 4, and/or those requiring a pump replacement that had documented pain relief with intrathecal morphine infusion. All but 3 cancer patients had chronic nonmalignant pain. The primary endpoint was to evaluate the cumulative accuracy of drug delivery as determined by the ratio of the delivered to programmed drug volume (DP ratio) for all refills per patient with a 90% confidence interval within 85% - 115%. The secondary endpoints consisted of efficacy, VAS, NRS, ODI, and serious adverse events (SAEs). Accuracy data was collected from 107 patients, 3 patients had their pumps explanted prior to their first refill due to pump incision infections.

Efficacy data were collected from 102 patients, 8 patients were excluded because their baseline NRS score was < 4. The mean per patient accuracy of drug delivery was 97.1% with a 90% confidence interval of 96.2% -

98.0%, and for all individual visits the accuracy of drug delivery was 97.2% with a 90% confidence interval 96.1% - 98.3%. Accuracy was maintained at a 90% confidence interval between 85% - 115% at each of the 6 months. Five of the 107 patients fell outside of the confidence criteria of 85% - 115%. There were 5 different flow rate groups and there were no significant differences for the accuracy of drug delivery noted between the flow rate groups ($P > 0.05$). The accuracy of drug delivery was dependent on residual volume where only the highest of the 5 residual volume groups (16 - 20 ml) was statistically different compared to the other 4 residual volume groups that had a higher consistency of accuracy ($P < 0.05$). There was a statistically significant reduction in pain (VAS, NRS) ($P < 0.0001$) and disability (ODI) ($P = 0.0001$ to $P = 0.0041$) each month. Decreases in pain and disability were reported at 68.4% of patient visits. No unanticipated adverse events or device complications were reported. The authors concluded that the Prometra pump provides an accurate, effective, and safe system for intrathecal administration of morphine sulfate for treatment of chronic intractable pain.

There were 43 side effects in 28 of the 110 patients (25.5%), the most common being procedural pain, nausea, and implant site pain and/or edema. The rest of the side effects included infection, hematoma, pain, abscess, nausea and vomiting, drug withdrawal syndrome, lumbar puncture syndrome, and temporary paralysis which resolved with treatment. 18 of the 110 patients (16.4%) experienced device-related complications that consisted of catheter migration, catheter tear or break, pump migration, catheter occlusion, and pump flip. Surgery was required in 13 of the 110 patients to replace or correct the catheter due to migration, occlusion, and tears or breaks. The authors concluded that the Prometra programmable IT pump system provided accurate drug delivery in 95.3% (102 of 107) of patients with significant improvement in pain and function.

The purpose of Veizi et al's study (201) was to examine the effect of intrathecal co-administration of bupivacaine with opioids during the initial phase of opioid titration and up to one year after implantation of an IDDS. In a retrospective manner, data from 126 consecutive noncancer intractable pain patients were collected and analyzed. Pain intensity, amount of oral opioids, dose, rate, concentration of IT opioids and bupivacaine, and number and type of IT medication used were recorded at preimplant and post implant at 3, 6, and 12 months postimplant.

There were 2 cohorts derived from 171 IDDS patients of which 45 were excluded due to cancer pain, only baclofen infusion, opioids not infused, initial opioid was not morphine or hydromorphone, or a combination that did not include local anesthetics. 72 patients were infused with an opioid (O) (morphine or hydromorphone) as a single medication and 54 patients were infused with an opioid (O) (morphine or hydromorphone) and a local anesthetic bupivacaine (O+B). In the O cohort there were 42 with failed back surgery syndrome (FBSS), 5 with complex regional pain syndrome (CRPS), 6 with spinal cord pathology, 3 with visceral pain, and 16 patients with various types of pain, including postherpetic neuralgia, diabetic peripheral neuropathy, and vertebral fracture due to severe osteoporosis. From the O+B cohort 27 patients had FBSS, 5 had CRPS, 3 had spinal cord pathology, 4 had visceral pain, and 15 had various types of chronic and neuropathic pain. The IT therapy was analyzed over the initial 12 months postimplant. During the first year postimplant, there were changes in the medications. This was seen in particular in many of the patients in the IT O cohort where bupivacaine was added at either 3, 6, or 12 months. Nevertheless, an intent-to-treat analysis was performed and patient data were analyzed based on the initial assigned treatment group.

There was a significant reduction in pain intensity in the O and O+B groups at 12 months. The O group average pain improved significantly from baseline with an average of 7.42 ± 2.1 to 5.85 ± 2.8 ($P < 0.001$) at 12 months. The O+B group average pain also improved significantly from baseline with an average of 7.35 ± 2.0 to 5.03 ± 2.4 ($P < 0.001$) at 12 months. There was no significant difference in the degree of pain relief between the 2 groups ($P = 0.09$). The combination of opioids with bupivacaine (O+B) from the start of IT infusion treatment resulted in a reduced progression of opioid dose escalation in comparison to patients started with opioids (O). The rate of increase of IT opioids in the O group at 12 months was 535 ± 180% compared to the O+B group where the dose increase was significantly lower at 185 ± 85% ($P < 0.004$).

In both groups, there was a statistically significant decrease in oral opioid consumption compared to preimplant doses. The average morphine equivalent daily dose (MEDD) at baseline was 138 ± 112 and 126 ± 87 mg/day in the O and O+B groups respectively. Oral opioid doses in the O cohort decreased to postimplant values of 100 ± 173 mg at 3 months, 81 ± 104 at 6 months, and 64 ± 93 at 12 months ($P < 0.001$). The average MEDD in the O+B cohort at postimplant also declined

significantly to 126 ± 87 mg/day at 3 months, 108 ± 124 mg/day at 6 months, and 72 ± 102 mg/day at 12 months (P = 0.0.01). There was no difference in the opioid dose decrease between the O and O+B groups over the 12 months (P = 0.18).

Adverse effects resulting from the addition of bupivacaine include numbness, paresthesia, and weakness; bowel and bladder dysfunction, and rarely, hypotension, all of which are reversible by decreasing the dose of bupivacaine. No major adverse effects were reported.

The authors in this study demonstrated that the addition of bupivacaine to opioids from the onset of IT infusion therapy resulted in the reduction of opioid dose escalation in patients with chronic nonmalignant pain. In addition, there was a significant reduction in the use of oral opioids.

Hamza et al (202) evaluated 61 consecutive patients in a 3 year prospective study to determine the efficacy of low dose intrathecal opioids for the treatment of chronic noncancer pain. All 61 patients underwent an IT trial with opioids after being weaned to 50% of their baseline over 3 to 5 weeks. Fifty-eight of the patients had a successful trial and underwent IT pump implantation.

The implanted patients were assessed at baseline and at 6 month intervals post operatively ending at 36 months. At baseline and at each 6 month follow up the 58 patients completed the Brief Pain Inventory (BPI) which determined worst pain, average pain, physical function, and behavior. The Patient Global Assessment (PGA) was also completed to assess pain and function at baseline and at the 6-month follow up visits. Oral opioids were recorded as morphine equivalents at baseline, 3 months post implant and every 6 months post implant up to 36 months. IT opioids were also documented as morphine equivalents at each of the 6 month follow up visits.

There was substantial improvement in all of the BPI outcome measures (P < 0.001) from baseline to 36 months which encompassed BPI worst and average pain, BPI physical function scale (BPI-PFS), BPI behavior scale (BPR-BS), and BPI enjoyment scores. The PGA from baseline to 36 months demonstrated a reduction in pain by 65.2% (range 20-95%, SD [standard deviation] = 21.8%); and an improvement in function by 42.7% (range 10-80%, SD = 19.4%). Although there was a statistically significant increase in the IT dose from 6 to 36 months (P < 0.001), the average increase was only 11.4% over 3 years. Oral consumption of opioids were considerably reduced at 3 months post implant compared to baseline (P < 0.001) from 126.71 mg/day (95% confidence interval [CI] = 100.83-152.58 mg/day, standard error [SE] = 12.92) to 3.80 mg/day (CI = 2.01-5.60, SE = 0.90). This was a 97% reduction in the use of oral opioids at 3 months which remained unchanged over the 3 years of follow up.

The side effects reported in this study consisted of wound infection (5%), peripheral edema (3%), pruritus (5%), and seroma (3%). Two patients with wound infection were explanted and re-implanted 6 weeks later.

This study showed that long term low dose IT opioid pump therapy can be very effective in controlling chronic noncancer pain. There was substantial and sustained pain relief and functional improvement. In addition, there was only a small increase in IT opioids over the 3 year period and a large reduction in the use of oral opioids.

In a consensus guideline statement (248), the panel unanimously agreed that appropriate patient selection is vital to achieving successful outcomes with chronic intrathecal analgesic therapy; however, specific patient selection indications for implantation with IDDS are not supported by rigorous, literature-based scientific data. The ultimate determination to proceed with intrathecal therapy requires the resolution of 2 principal overlapping decisions—who to implant and when to implant the patient with an internalized device. Although it is challenging to ascertain optimal timing for the initiation of intrathecal therapy, various indicators may signal that a patient is "ready" for this aggressive form of treatment. To optimize clinical practice in the absence of evidence-based guidance or validated tools for chronic intrathecal analgesic therapy patient selection, the panel assembled a set of arbitrary, multidisciplinary issues that merit consideration during individualized risk-versus-benefit evaluations (Table 12).

By utilizing a multifaceted approach—with consideration of a patient's physical, psychological, and social characteristics—practitioners can determine the appropriateness of initiating IT therapy, thus minimizing the potential for treatment failure, unacceptable adverse effects, and excess mortality. Related psychological factors influencing patient selection and appropriate timing for intrathecal therapy initiation can be appraised during an interactive patient interview, a step in the patient selection process that the panel deemed crucial to the success of therapy.

Overall, the studies have shown a long-term benefit from intrathecal infusion devices used for chronic

Table 12. *Key considerations for selection and implantation of patients with noncancer pain for intrathecal therapy.*

Contraindications for Immediate Trial/Implant	Indications to Proceed With Trial/Implant
• Immunocompromised patients at high risk for infection or patients presenting with an active infection	• An appropriate diagnosis of the patients pain has been established
• Patients presenting with severe psychological conditions, including untreated significant addiction; active psychosis with delusional/ hallucinatory components; major uncontrolled depression/anxiety; active suicidal or homicidal behavior; serious cognitive deficits; or severe sleep disturbances	• Chronic pain results in significant interference with activities of daily living, including ability to work, and overall quality of life
• Current or anticipated lack of insurance coverage or means to pay out-of-pocket for both surgical implantation and ongoing medication refills/reprogramming	• Preexisting medical comorbidities are well-controlled and appropriate disease-specific guidelines are followed pre- and post-implantation
• Inability to comply with medication refill schedule due to geographic limitations	• Patients presenting without any severe or uncontrolled psychological conditions
	• Patient has tried and failed to achieve sufficient analgesia with less invasive therapies
	• Patients in which oral opioid therapy is contraindicated (eg, a patient who has difficulties managing his/her medications, an individual with certain comorbid conditions in which oral opioids have the potential for severe adverse effects)

non-cancer pain. Although the life span of patients should be considered several decades after pump implants, studies seem to show a stable rate of analgesia at least for less than 10 years. This effect may not be as pronounced once the period is extended to more than a decade. Also, the formation of inflammatory masses in the form of granulomas is a major deterrent with this modality. As previously thought, the granuloma formation does not depend on the drug itself and has been seen with morphine as well as baclofen infusions. A Canadian study demonstrated the cost effectiveness of intrathecal infusion devices. Kumar et al (249) looked at the cost of implanting a programmable drug delivery pump vs. conservative treatment of chronic pain. Their population consisted of failed back syndrome patients. Successful outcomes were measured using the pain scale, ODI, and QOL. The cumulative costs for intrathecal drug delivery during a 5-year period were $29,410, as opposed to $38,000 for conservative treatments. High initial costs of equipment required for intrathecal drug delivery were recovered by 28 months. After this time, managing patients with conservative treatments became more expensive for the remainder of the follow-up period. The ODI showed a 27% improvement for patients in the intrathecal drug delivery group, compared with a 12% improvement in the control group. This is an important finding and may help justify the initial cost of the implantable pump system. However, considering the life of the programmable pump, there is obviously a high added cost for maintaining this treatment option beyond the initial life of the pump for the patient's life span.

The limitations of this systematic review include the paucity of literature. There were no randomized trials available meeting the inclusion criteria. Furthermore, there are also very few observational studies. Systematic reviews in interventional pain management are signs of progress in the effort to keep pace with advances in health care innovations. Systematic reviews have been growing at a rapid pace in interventional pain management (250,251). Systematic reviews are at the core of evidence-based medicine which is a shift in medical paradigms that acknowledges that intuition, unsystematic clinical experience, and pathophysiologic rationale are insufficient grounds for clinical decision-making (120,252,253). In the hierarchy of strength of evidence for treatment decisions, N of 1 randomized controlled trials (RCT) occupy the top place, followed by systematic reviews of randomized trials, systematic reviews of observational studies, and finally unsystematic clinical observations. Thus, observational studies and their systematic reviews are lower in the hierarchy than the randomized trials and their systematic reviews. Randomized trials provide valuable evidence about treatments and other interventions. However, most of the research in clinical practice comes from observational studies (129,254,255). Randomized trials work by first assuming there is no difference between a new and an old or placebo treatment to prove the null hypothesis (256). In simplistic terms, standard RCTs

are designed to show that treatments do not work, rather than to demonstrate that treatments do work. Numerous criticisms, politics, and a lack of understanding of randomized trials have resulted in allegations that the research performed to test new treatments has often been of poor quality. Thus, clinicians have criticized the research establishment for failing to provide answers to relevant clinical problems of everyday practice (257,258). Most questions in medical research are investigated by observational studies (19,259-277) which are more likely to provide an indication of daily medical practices (278). Proponents of observational studies, therefore, believe 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 (271). Thus, observational studies and RCTs can be viewed in the setting of modern clinical research as expressions of the steps of observation and experimentation that form the basis of scientific methodology. The observational step is used to uncover patterns and formulate hypothesis regarding cause-and-effect relationships, followed by the experimentation step in which the hypotheses formed in the observational setting are confirmed or refuted in an experiment in which the independent variables are controlled by the experimenter (271,279,280). A major drawback of observational research is that of poor reporting, as it results in an inability to assess the strengths and weaknesses of the investigations (129,255,279,280). These deficiencies can be overcome by an assessment of the methodological quality of observational studies. There are several instruments for methodological quality assessment of randomized trials (253). In this systematic review, we have utilized West et al's (281) criteria as described by the Agency for Healthcare Research and Quality (AHRQ) evidence report of technology assessment. They assessed 19 systems relating to observational studies or investigations prior to developing the criteria. Consequently, we believe that this systematic review provides appropriate information.

The major argument made by researchers is that interventions such as intrathecal implantables may not be performed in a double blind manner. However, they can be performed as equivalence or non-inferiority trials with randomization, but without blinding. In fact, multiple studies describing interventions have been performed in this manner (259,262,264,282-299).

5.0 Conclusion

In summary, the evidence for the use of intrathecal opioid infusion systems for the treatment of chronic non-cancer pain is limited based on this systematic review with both short-term and long-term pain relief and functional improvement. The conclusions rendered from this systematic review are based on the absolute lack of literature and a limited number of moderate quality studies. Therefore, there is a great need for more robust clinical research to have a clearer understanding on the use of intrathecal opioid infusion systems for the treatment of chronic non-cancer pain. In addition to more vigorous clinical research, it is vitally important that those who involve themselves in the assessment of medical and surgical treatments for any medical disorder do so in an honest, responsible, and accountable way with integrity, independence, transparency, consistency, and without any secondary gain.

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Author affiliations

Dr. Frank Falco is Adjunct Associate Professor, Temple University Medical School, Philadelphia, PA; Director, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Medical Director, Mid Atlantic Spine & Pain Physicians, Newark, DE.

Dr. Vikram Patel is Medical Director of 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, Charleston, WV, and Clinical Professor, Anesthesiology, West Virginia University School of Medicine, Charleston, WV.

Ms. Geffert is Director of Research and Education and Administrative Assistant at Mid Atlantic Spine & Pain Physicians of Newark, DE, and Fellowship Coordinator at Temple University Hospital, Philadelphia, PA.

Dr. Zhu is Adjunct Assistant Professor, Temple University Medical School, Philadelphia, PA; Faculty, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Attending Physician, Mid Atlantic Spine & Pain Physicians, Newark, DE, and Elkton, MD.

Dr. Onyewu is Attending Physician, Mid Atlantic Spine & Pain Physicians, Newark, DE, and Elkton, MD; Faculty, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Adjunct Assistant Professor, Temple University Medical School, Philadelphia, PA.

Dr. Coubarous is Attending Physician, Mid Atlantic Spine & Pain Physicians, Newark, DE.

Dr. Howard Smith is Professor & Academic Director of Pain Management, Albany Medical College, Department of Anesthesiology, Albany, NY.

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.

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