Implantable pain therapy: Intrathecal infusions

Plain language summary

There are many treatments for persistent pain. These include medications, physiotherapy, psychological therapy and nerve blocks. In a few patients these treatments may not work or may cause unpleasant effects. For this small group of patients one treatment that has been tried is intrathecal infusion (ITI) of medications. This involves implanting a pump containing the medication under the skin over the stomach. This pumps medication into the fluid around the spinal cord.

This review updated a previous review of the research. This was to find out whether ITI is helpful for patients with persistent pain that is not due to systemic inflammatory conditions, vascular insufficiency, haematological disorders or cancer. One evidence-based guideline and three randomised controlled trials were found and included in the review.

Based on these studies and the previous review, the effect of ITI of opioids (narcotics) and ketorolac (anti-inflammatory) is unclear. There is low quality evidence that ITI of gabapentin is not helpful. There were no studies of baclofen or ziconotide. Most studies did not look at quality of life, return to work, medication use or healthcare use.

The studies found possible harms from ITI, including an increased risk of death. Less serious harms include medication problems, such as nausea, dizziness, sleepiness, and headache, and pump problems, such as pump breakdown, pump movement and infection.

Research report#: 115-0415-R03

Implantable Pain Therapies: Intrathecal Infusions

Ornella Clavisi, Melissa Chee, Loyal Pattuwage, Anneliese Synnot

30 April 2015
Research report#: 115-0215-R04

ISCRR is a joint initiative with the following three partners:

This research report was prepared by:

Ornella Clavisi, Melissa Chee, Loyal Pattuwage, Anneliese Synnot: National Trauma Research Institute, Monash University.

For Transport Accident Commission and WorkSafe

This is an updated of a previous report (Donoghue 2011)

Accompanying documents to this report

***Title**: Implantable Pain Therapies: Intrathecal Infusions*

- *Technical report (Report number: 115-0215-Z04)*
- *Plain language summary*

TABLE OF CONTENTS

EVIDENCE REVIEW SUMMARY

Implantable Pain Therapies: Intrathecal Infusions

Purpose

The Transport Accident Commission (TAC) and the WorkSafe (WS) requested a review of the evidence to determine whether intrathecal (IT) infusions are an effective treatment compared to placebo or active treatment in the treatment of persistent non-cancer pain. This review sought to find the most up-to-date, high quality source of evidence to answer the following questions:

- In what conditions are IT infusions indicated?
- What is the effectiveness of IT infusions on persistent spinal pain in these conditions?
- What is the effect of IT infusions on function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation?
- In what patient groups/conditions are IT infusions contraindicated?
- What are the risks associated with use of IT infusions?
- What are the impact of training and/or experience of practitioners on patient outcomes?

Rationale

The rationale for this evidence review summary is to ensure funding decisions made regarding the use of IT infusions are evidence-based and in the best interests of injured Victorians.

New research relevant to IT infusions is regularly being published. This review is important for WS/TAC as it provides an independent, thorough search and quality assessment of the peer-reviewed literature in this area. This can then be used to support funding decisions regarding this treatment. This review is an update of a review that was first conducted in 2011. As such, most included studies were conducted between 2011 and April 2014 (date of latest searches). The search can also be repeated in the future to incorporate new evidence as it arises. However, we note that the clinical use of IT infusions in Victoria is declining.

Methods

Systematic review methods were used. A comprehensive search of Medline, Embase, the Cochrane Library, and All EBM was undertaken in April 2014 to identify relevant research. Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were independently screened for inclusion by two authors. In this review studies were only included if they were evidence-based guidelines (EBGs),

systematic reviews (SRs), health technology assessments (HTAs), randomised controlled trials (RCTs) and controlled clinical trials (CCTs) that investigated the effects of IT infusions compared with placebo (or other active treatments) in patients with persistent pain. Evidence that met the selection criteria was reviewed to identify the most up-to-date and comprehensive source of evidence. Individual studies and secondary research reports were assessed for risk of bias and the quality of evidence assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Schunemann 2013).

Research findings and implications

We searched for EBGs, SRs, HTAs, RCTs and CCTs that evaluated the effect of IT infusions for the treatment of persistent non-cancer pain. Overall we identified:

- 1 RCT and 1 EBG for the use of analgesics (opioids)
- 2 RCTs for the use of other medications (ketorolac and gabapentin)

In what conditions are IT infusions indicated?

Based on the evidence, the indication for IT use is unclear. The patient groups recruited by the studies were broad, e.g. patients with chronic pain receiving IT morphine for at least 6 weeks (Eisenach 2010) or adults with non-cancer pain eligible for IT infusion (Rauk 2013, Raphael 2013). Furthermore, the majority of studies did not report the origin or type of pain experienced by the patients (e.g. in Manchikanti 2013). Predominantly, they were described as 'patients with chronic non-cancer pain' or 'patients with chronic pain of nonmalignant etiology'.

What is the effectiveness of IT infusions on persistent pain and other patient relevant outcomes?

Analgesics (Opioids)

The results of studies assessing the effectiveness of opiods on pain and function were mixed. In addition, the quality of the evidence was rated as very low. As such, we are uncertain about the effect of analgesics (opioids) in patients with persistent non-cancer pain on pain and function. No studies were identified that measured other pre-specified outcomes (i.e. quality of life, return to work, medication use and healthcare utilisation).

Anti-spasmodic drugs (baclofen)

No primary or secondary research was identified about the effect of anti-spasmodic drugs in patients with persistent non-cancer pain.

Calcium-channel antagonists (ziconotide)

No primary or secondary research was identified about the effect of calcium-channel antagonists in patients with persistent non-cancer pain.

Other medications

Ketorolac

There is very low quality evidence indicating IT ketorolac is no better than placebo in reducing pain and medication use or increasing function and quality of life in patients with

persistent non-cancer pain. Due to the very low quality of the evidence, we are therefore uncertain about the effect of ketorolac in patients with persistent non-cancer pain on pain. No studies were identified that measured other pre-specified outcomes (i.e. function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation).

Gabapentin

There is low quality evidence indicating IT gabapentin is no better than placebo in reducing pain and medication use or increasing function and quality of life in patients with persistent non-cancer pain. No studies were identified that measured other pre-specified outcomes (i.e. return to work and healthcare utilisation). While a rating of low quality evidence implies that further research is likely to change the effect estimate, we note the authors of this study reported no plans for further research into gabapentin.

In what patient groups/conditions are IT infusions contraindicated?

This was not reported by any of the included studies

What are the risks associated with use of IT infusions?

The risks identified for IT infusions include:

Analgesics (opioids)

While the vast majority of complications for IT opioid therapy were minor (such as catheter kinking, infection and nausea), some serious complications such as death (Coffey 2009) and granuloma formation (Miele 2006) were reported.

Anti- spasmodic drugs (baclofen)

No evidence was identified to allow an assessment of the risks associated with anti-spasmodic drugs.

Calcium-channel antagonists (ziconotide)

No evidence was identified to allow an assessment of the risks associated with calcium-channel antagonists.

Other medications

Ketorolac

The following symptoms were reported after injections: numbness in left leg for less than two hours, mild sedation, mild dizziness, hot sensation in the back, headache, urinary retention and hives. However, the incidence of adverse events did not differ between ketorolac and saline injection.

Gabapentin

No adverse events were reported that can definitely be related to gabapentin. A total of 121 adverse events were reported as being possibly and 9 adverse events as being probably related to gabapentin respectively. The most common drug related adverse events were nausea, somnolence, headache, dizziness, fatigue and peripheral edema.

What are the impact of training and/or experience of practitioners on patient outcomes?

The issue of training was not explored in any of the included studies.

Report no: TBA
Date: 30 April 2015

BACKGROUND

Implantable pain therapies (IPTs) have been used to treat patients for a variety of pain disorders. They include a range of neurostimulation procedures and IT infusions of analgesic, local anaesthetic, anti-spasmodic and other pharmacological agents. In order to develop and update policies for the use of IPTs in patients with persistent pain, the Transport Accident Commission and WorkSafe (TAC/WS) requested an update of the Evidence Reviews of IPTs published in 2011 (Donoghue 2011).

The focus of this review is to evaluate the effectiveness and safety of implantable IT infusions in patients with persistent pain following transport-related or workplace injuries. The effect of IT infusions on pain due to systemic inflammatory conditions, vascular insufficiency, haematological disorders or cancer is outside the scope of this review.

Intrathecal (IT) infusions

For a small proportion of patients with non-cancer pain who do not experience sufficient pain relief or have intolerable side effects with conventional treatments (such as oral medications and allied health interventions), IT infusions may be an effective treatment. This involves implanting a specialised device (pump) subcutaneously in the abdominal region. Tubes from the pump are inserted into the IT space around the spine which contains cerebrospinal fluid that bathes the spinal cord. Medications are then delivered via the tubes to where it has its action, therefore eliminating side effects of taking the drug orally or parenterally.

According to the Australian and New Zealand College of Anaesthetists' guidelines, IT delivery of drugs for long term pain management can be used for a small, carefully selected subgroup of patients. They recommend that IT infusion be used as last line therapy in those whose pain is not adequately controlled by less invasive measures (e.g. physical therapy, psychological therapy, oral and parenteral medication and neural blockade) or where other routes of medication cause side effects (Australian and New Zealand College of Anaesthetists 2005, Australian and New Zealand College of Anaesthetists 2013). They also caution the use of IT infusions in patients where psychological factors are considered to be a major pain modifying factor and recommend that psychological evaluation be done on all patients before starting IT treatment.

Several medications, diverse in their mechanisms of action, have been reported for use in IT pumps and can be grouped into the following categories –

- analgesics (opioids),
- anti-spasmodic drugs (baclofen),
- calcium channel blockers (ziconotide), and
- other medications (including ketorolac and gabapentin)

Within these categories, medications can be administered on their own or combined with other medications or other implantable therapies, either from the same category or a different category.

In Australia, only baclofen is licensed for long term IT use for spasticity. All other IT infusion medications are prescribed/administered off label under the Australian Therapeutic Goods Administration's (TGA) "Access to Unapproved Therapeutic Goods" scheme.

Background information relating to the different drug categories used for IT infusion is provided below.

1. Analgesics (opioids)

Opioids are medications usually used for pain relief. Common opioids are morphine, oxycodone and codeine. The mechanism of action of opioids is through the attachment to proteins called opioid receptors, which are present in the central nervous system. Opioids used for IT treatment in countries other than Australia include morphine, hydromorphone, fentanyl, buprenorphine and sufentanil. These drugs have not been approved by the Australian TGA for IT use.

2. Anti-spasmodic drugs (baclofen)

Baclofen is a GABA-β receptor agonist that acts through the central nervous system to relax muscles. GABA (or gamma-aminobutyric acid) is the main inhibitory neurotransmitter used in the nervous system that regulates neuronal signalling. The mechanism of action for baclofen is to bind to pre-synaptic GABA-β receptors, which in turn inhibits the release of neurotransmitter (GABA) onto the neurons of the spinal cord that cause the sensation of pain. Post-synaptic binding of baclofen to GABA-β receptors results in a reduction in neuronal excitability which is thought to contribute to spasticity. Baclofen can be administered through an IT pump for the treatment of severe pain and disability, secondary to spasticity.

3. Calcium channel blockers (ziconotide)

Ziconotide is the synthetic equivalent of a pain-relieving chemical found in the venom of a certain type of sea snail. It is a calcium channel antagonist which is thought to inhibit neurotransmitter release from N-type calcium channels present on neurons located in the spinal cord. In Australia, ziconotide is classed as an experimental drug and is not approved for IT use by the TGA.

4. Other medications

Other medications that have been used intrathecally for the treatment of chronic, severe pain include clonidine, bupivacaine, sufentanil, fentanyl, midazolam and gabapentin. Of these only two have been tested in RCTs: ketorolac and gabapentin.

Ketorolac

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) which has inhibitory effects on cyclooxygenase (COX), an enzyme responsible for the production of prostanoids (prostaglandins, prostacyclin and thromboxane) which relieve pain and inflammation in the body. Ketorolac is an experimental IT drug which has only recently been tested for chronic pain in humans and animals (Eisenach 2010). The drug was initially administered systemically as an analgesic for postoperative pain. As severe chronic pain may originate in the central nervous system, an attempt was made to test IT ketorolac to see if the central nervous system was also a site of action in the body. In Australia, ketorolac has not been approved by the TGA for IT use.

Gabapentin

Gabapentin ([1-(aminomethyl) cyclohexaneacetic acid]) is an antiepileptic drug that is commonly used to treat patients with neuropathic pain. Although several studies have focused on the analgesic action of gabapentin on the spinal cord, its mechanism of action is not fully understood. IT administration of gabapentin has been shown to inhibit pain in rodents (Cheng 2000, Kaneko 2000, Takeuchi 2007). The effect of IT gabapentin on humans has not been established (Rauck 2012). In Australia, gabapentin has not been approved by the TGA for IT use.

QUESTIONS

This review sought to find the most up-to-date, high quality sources of evidence to answer the following questions:

1. In what conditions are IT infusions indicated?

2. What is the effectiveness of IT infusions on persistent spinal pain in these conditions?

3. What is the effect of IT infusions on function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation?

4. In what patient groups/conditions are IT infusions contraindicated?

5. What are the risks associated with use of IT infusions?

6. What are the impact of training and/or experience of practitioners on patient outcomes?

METHODS

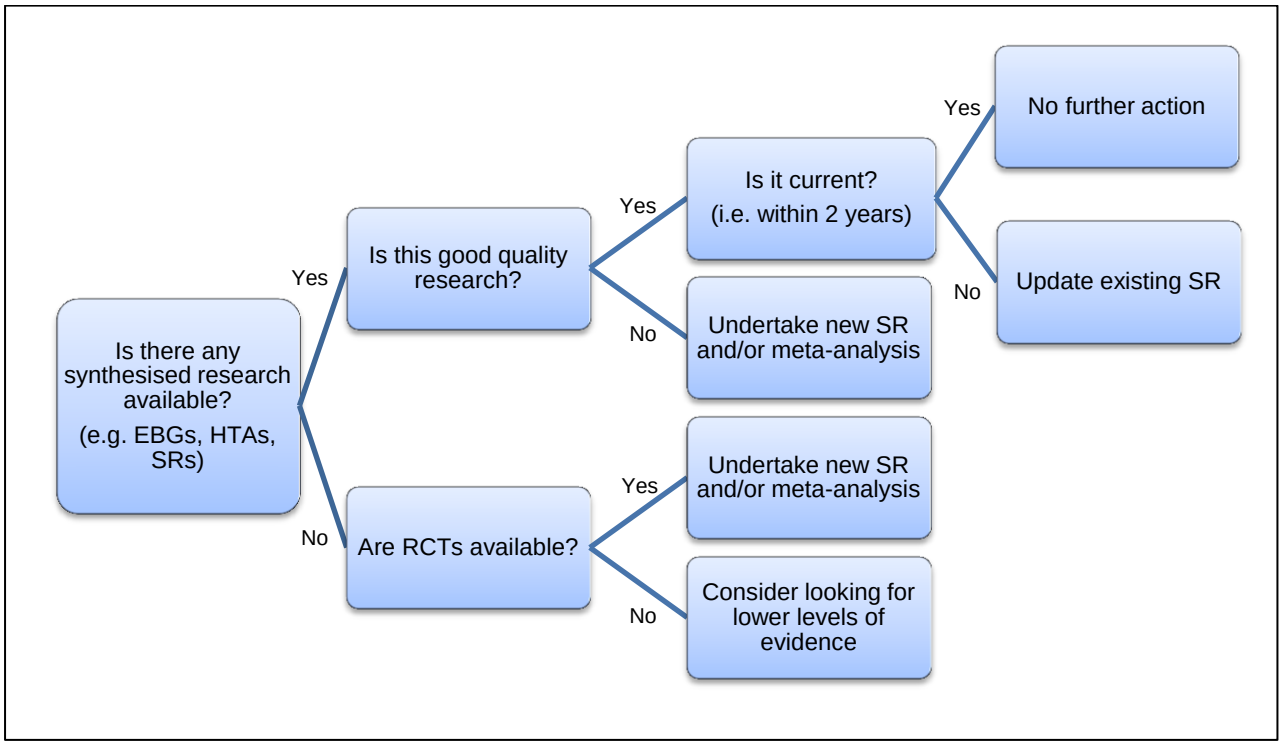
Methods are outlined briefly within this section. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2 that are located in the Technical Report accompanying this document.

A comprehensive search of Medline, Embase, the Cochrane Library, and All EBM was undertaken in April 2014 to identify relevant research (i.e. EBGs, SRs, HTAs, RCTs and CCTs). Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were screened for inclusion using specific selection criteria (see Appendix 2, Table A2.1). In this review, studies were only included if they were EBGs, SRs, HTAs, RCTs or CCTs that investigated the effects of IT infusions compared with sham or active treatment in patients with persistent pain. Studies that met the selection criteria were reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine the risk of bias using a tool developed specifically for the review and the quality of the evidence according to the GRADE system (Schünemann 2013). For EBGs, the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool was used (see Appendix 2: Methods). Two reviewers conducted all screening and selection independently, results were compared and any discrepancies discussed and resolved.

The available evidence was mapped and the algorithm in Figure 1 was followed to determine the next steps necessary to answer the clinical questions.

Figure 1. Decision algorithm for study inclusion



Data on characteristics of all included studies were extracted and summarised (see Appendix 4, Technical Report). The most recent, comprehensive, high quality EBG or systematic review for each stimulation modality was used to address the questions posed above.

RESULTS

We conducted an electronic database search in April 2014. The search yielded 5675 potentially relevant citations after duplicate citations were removed. After reviewing titles and abstracts, 132 full texts were reviewed. The inclusion and exclusion criteria were then applied and 4 publications were selected and categorized according to stimulation modality (see Table 1). The algorithm in Figure 1 was then applied to determine the appropriate evidence to answer the clinical questions.

Table 1. Evidence map of identified studies by study-type

Types of Neurostimulation	Synthesised Studies			
	EBGs	SRs & HTAs	Primary studies	**Total**
Analgesics	1	-	1	2
Anti-spasmodic drugs	-	-	-	-
Other medications	-	-	2	2
				4

After application of the algorithm (Figure 1), the following evidence was identified for inclusion.

- Analgesics: One EBG and one RCT
- Other medications: One cross-over RCT and one RCT

1. ANALGESICS (OPIOIDS)

Evidence Identified

We identified one EBG (Manchikanti 2013) and one RCT (Raphael 2013) investigating the effect of implantable IT opioid therapy (see Table 1.1.1 and Table 1.1.2).

Study Characteristics

Manchikanti (2013) presented an EBG on interventional techniques for the diagnosis and treatment of chronic spinal pain, which included a section on implantable IT drug administration systems. Within this section, seven observational studies were included. Outcome measures included pain and function scores, medication use and level of activity. Pain relief and function were monitored over the short (<12 months) and long (>12 months) term.

Raphael (2013) presented an RCT which investigated long term efficacy of IT morphine delivered via an implantable device in patients with non-cancer pain for ≥ 12 months. Fifteen adults (aged 18 years or over) were randomly allocated in a 1:1 ratio to the intervention group (small reduction (20%) in morphine dosage every week during a 10-week follow-up) and control group (no change in morphine dosage). The causes of pain among the recruited patients include mechanical nociceptive caused by degenerative low back pain, visceral nociceptive due to post surgery abdominal pain and mixed nociceptive-neuropathic pain following failed back surgery syndrome. Primary outcomes were pain measured by visual analog scale (VAS) and withdrawal from the study. Secondary outcome measures were functional and psychological measures based on Oswestry Disability Index (ODI), Hospital Anxiety and Depression (HAD) scale and Coping Strategies Questionnaire (CSQ). Participants were evaluated at baseline and each week during participation in the study. Visual Analog Scale (VAS) and ODI were collected on a weekly basis. Hospital anxiety and depression scores and CSQ were collected fortnightly. This study investigated the long term efficacy of IT morphine by hypothesising that a reduction in the IT opioid dose would increase the level of pain intensity.

Risk of bias

The EBG (Manchikanti 2013) was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (Brouwers 2010) and scored relatively high on most domains. However, the studies included in the EBG were all observational in nature, with inherent methodological weaknesses. Further details of evaluation can be found in the Technical Report, Table A4.1.1 and Table A5.1.

Raphael (2013) randomised patients using computer-generated randomisation software and the allocation sequence was received in sequentially numbered, opaque and sealed envelopes. Both the patients and outcome assessors were blinded but the investigator was not. All patients were analysed using intention to treat analysis. Patients were randomized as a single block of 24 (instead of smaller blocks), which resulted in an uneven spilt of 10 patients in the intervention group and five in the control group. The dropout rates were also very high (47% overall or 70% in the intervention group) and the sample size was small (n=15). Furthermore the study was underpowered, as it required a sample size of 24 to

detect a difference in means of 1.2 SDs (unpaired t test) or a difference in proportions of 20% and 80% (Fisher's exact test). Further details of evaluation can be found in the Technical Report, Table A4.1.2 and Table A6.1.1.

Results

Effectiveness

Manchikanti (2013) provided a summary of the evidence identified for the use of implantable IT opioid therapy. Based on seven observational studies involving 706 patients, Manchikanti (2013) reported that the studies showed a long-term (>12 months) benefit (positive effect seen in five out of the seven studies) on pain from IT infusion devices used for persistent non-cancer pain.

Raphael (2013) reported that, within group VAS and ODI scores were significantly lower at baseline than at the last observation for the intervention group but not for the control group. However, these differences was not statically significant between groups (p = 0.070, 0.311, respectively). Additionally, there were no significant differences in change from baseline scores between groups for HAD anxiety or HAD depression (p = 0.653, 0.959, respectively).

Adverse Events

Complications related to IT therapy can be technical, biological or medication related. The vast majority of the complications reported in Manchikanti (2013) were minor technical or medication related (such as catheter kinking, infection and nausea) but some serious complications were reported. An increased risk of death was identified by the authors as likely related to the opioids, however the specific cause of death was not reported (Coffey 2009, Coffey 2010). Other serious complications included granuloma formation that the authors reported may have been related to the amount and concentrations of opiates (Miele 2006, Allen 2006, Coffey 2002). A granuloma can act like a space-occupying lesion damaging the spinal cord, often requiring major surgery to be removed. However, most granulomas improved with weaning off of the IT opiate, replacing it with preservative-free saline (Allen 2006).

Raphael (2013) did not report any adverse events.

Contraindications

Contraindications were not reported in any of the studies.

Effect of Training

Impact of training was not reported in the studies.

Discussion

The quality of the EBG in terms of scope, purpose and rigours methodology was high according to the AGREE criteria, but can be considered to be at moderate risk of bias due to the inherent methodological weakness of observational research.

Raphael (2013) was a relatively well conducted RCT, having low risk of bias for most of the elements for the 'risk of bias' assessment tool. However it was underpowered and had very high attrition rates.

Results for Raphael (2013) and Manchikanti (2013) were mixed. Some observational studies in the EBG found a positive effect on pain, whereas the RCT found no evidence of an effect on pain or function. Due to risk of bias concerns, small number of trials and conflicting results, the quality of the evidence for pain and function were rated as very low (see Table 1.1.3 for GRADE evidence profile). As such, we are very uncertain about the effect of analgesics (opioids) on pain and function in patients with non-cancer pain. No study measured the effect of opioids on quality of life, return to work, medication use or healthcare utilisation.

Table 1.1.1 Key information from most recent evidence based guideline for analgesics (opioids)

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation
Manchikanti (2013) An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations	**Patient/population:** Patients with persistent non-cancer pain (n= 706, seven observational studies) **Intervention:** Implantable IT drug administration systems **Control:** N/A (uncontrolled studies, observational studies) **Outcomes assessed:** • Pain intensity and relief • Medication consumption • Level of activity • Quality of life • Complications	EBG	"Overall, all the observational studies have shown a long-term benefit from IT infusion devices used for chronic non-cancer pain." (pg S179).

Table 1.1.2. Key information from most recent primary study for analgesics (opioids)

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation
Raphael (2013) Randomised, double-blind controlled trail by dose reduction of implanted IT morphine delivery in chronic non-cancer pain	**Patient/population:** Patients with implanted IT reservoirs of programmable type receiving IT morphine for non-cancer pain and having had infusion for ≥ 12 months (n=15) **Intervention:** Small reduction (20%) in morphine dosage every week during a 10-week follow-up **Control:** No change in morphine dose **Outcomes assessed:** Primary outcomes were visual analogue scale (VAS) pain score change and withdrawal from the study due to lack of efficacy	RCT	This RCT was relatively well conducted except for the high drop-out rates (7 out of 10 in the intervention group). Owing to the small number of patients who had completed the study (n=3 in the intervention group and n=5 in the control group), further studies are warranted.

Table 1.1.3 GRADE evidence profile for analgesics (opioids)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	20% dose reduction in morphine	No change in morphine dose	Relative (95% CI)	Absolute	
Visual analog scale (follow-up 10 weeks; measured with: 0-10 scale; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3	5	Not estimable because only median (range) were given		⊕OOO VERY LOW
Oswestry disability index (follow-up 10 weeks; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3	5	Not estimable because only median (range) were given		⊕OOO VERY LOW

[1] High attrition bias (7 out of 10 in the intervention group)
[2] Small sample size (n=15)

2. ANTI-SPASMODIC DRUGS (BACLOFEN)

Evidence Identified

No new published studies on anti-spasmodic drugs were identified since the last review (2011). As such, we considered the evidence from pre-2011 studies that were found in the last review.

Searches yielded one EBG (Hooten 2013), one HTA (Accident Compensation Corporation 2005) and one non-systematic literature review (Jadad 2001). However, the EBG did not identify any controlled studies that met the inclusion/exclusion criteria for the report. Thus it was excluded. The HTA and Jadad (2001) were non-systematic literature reviews and hence they were also excluded for this review.

In light of the lack of primary or secondary research found that address the use of anti-spasmodic drugs for persistent pain, we are unable to report any findings/conclusions regarding use of this intervention for the treatment of persistent pain.

3. CALCIUM CHANNEL BLOCKERS (ZICONOTIDE)

Evidence identified

No new published studies on calcium channel blockers were identified since the last review (2011). As such, we considered the evidence from pre-2011 studies that were found in the last review.

Searches yielded one SR (Turner 2007) for the use of calcium channel blockers in the treatment of persistent, intractable pain. But the authors of the SR found that 'no studies for ziconotide met the inclusion criteria for either effectiveness or the complications review'. Thus this SR was excluded for this review.

In light of the lack of primary or secondary research found that address the use of calcium channel blockers for persistent pain, we are unable to report any findings/conclusions regarding use of this intervention for the treatment of persistent pain.

4. OTHER MEDICATIONS

Evidence Identified

No new published studies on other medications were identified since the last review (2011). As such, we considered the evidence from pre-2011 studies that were found in the last review.

The search yielded one crossover RCT comparing IT ketorolac with IT saline (placebo) in patients with chronic leg or back pain (Eisenach 2010). We also identified one RCT investigating the effect of IT gabapentin for intractable non-cancer pain (Rauck 2013).

Ketorolac

Study Characteristics

The publication by Eisenach (2010) reported three clinical trials: (1) open label study to assess tolerability of IT ketorolac (2) crossover RCT to compare IT ketorolac against normal saline (3) postoperative pain study to assess effectiveness of ketorolac in relieving post-operative pain. The first trial was a dose escalation study that assessed adverse effects and safety of ketorolac, without a control group. The third trial investigated women undergoing vaginal hysterectomy under spinal anaesthesia. Both these trials did not meet the inclusion criteria for this review. The second study (the crossover RCT) which compared IT ketorolac with placebo (i.e. saline) is relevant for this review and thus is discussed here.

Twelve patients with chronic pain who were receiving IT morphine via an implanted pump for at least six weeks were randomised to receive either 2mg of preservative free ketorolac or saline in the first visit and swapped over in the second visit. The study assessed pain intensity and unpleasantness using VAS at 15 minutes, 30 minutes, one, two and four hours after the IT injection via the pump. The second visit occurred between one week and three months post the initial visit.

Risk of Bias

Eisenach (2010) used computer generated sequence to randomise patients but did not report whether the sequence was concealed. The author also reported that the trial was 'double blind' and used a person not involved in the patient care or evaluation to prepare the injection; nevertheless they failed to precisely state how the treating physician was blinded to the intervention. It was reported that the outcome assessors were blind to the intervention.

Results

Effectiveness

Both pain intensity ($p = 0.01$) and unpleasantness ($p = 0.02$) decreased with time after IT injections but there was no difference between ketorolac and saline, and there was no significant interaction between treatment and time. Similarly, the proportion of subjects who experienced at least 30 or 50% pain relief after IT injection did not differ between the ketorolac and saline groups. Neither ketorolac nor saline altered pain intensity or unpleasantness for thermal testing.

Adverse Events

Four subjects reported new symptoms (detailed below) after ketorolac injection and five after saline.

After ketorolac injection, two subjects described mild sedation lasting less than two hours, one reported mild dizziness lasting less than 30 minutes, and one experienced a hot sensation in the back, headache, urinary retention, and hives beginning four days after injection and lasting less than four hours.

After saline injection, two subjects described mild sedation lasting less than one hour, two had mild nausea lasting less than one hour, and one had a mild headache lasting less than two hours.

Contraindications

Contraindications were not reported.

Effect of Training

Impact of training was not reported.

Discussion

The evidence available from Eisenach 2010 was of very low quality, due to concerns about risk of bias and very small participant numbers (see Table 4.1.2 for GRADE evidence profile). This study recruited patients who were already on IT morphine for chronic pain via an implanted device and did not find any significant difference in reduction of pain intensity or unpleasantness when IT ketorolac (treatment) was compared to saline (placebo). However, as the quality of this evidence was rated as very low, it means we are uncertain about the effect of ketorolac on pain. This study did not measure the effect of ketorolac on function, quality of life, return to work, medication use or healthcare utilisation.

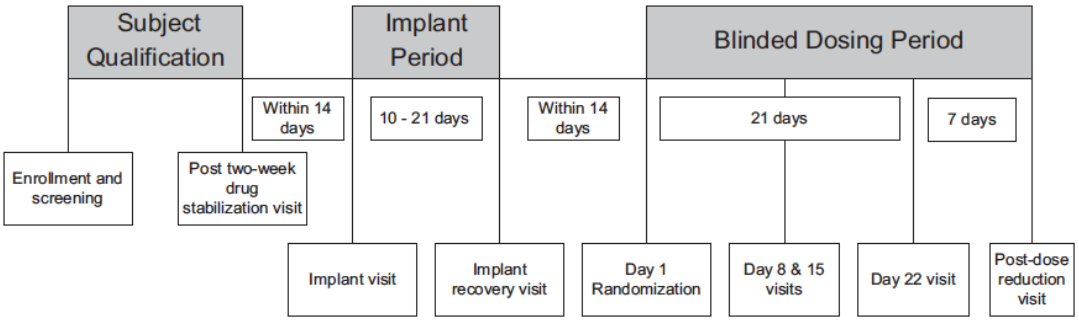
Gabapentin

Study Characteristics

Rauck (2013) recruited 171 patients who were implanted with an IT device of which one subject was assigned to receive open label study drug due to a randomisation error. Therefore, 170 were randomised to treatment groups. These patients had persistent intractable pain below the neck for a minimum of 1 year who had failed one or more systemic pain medications and had an average daily score of >=5 on the numerical pain rating scale (NPRS). Patients were initially implanted with a IT drug delivery system and then randomised into one of four treatment groups, placebo (0.9% sodium Chloride injection) or gabapentin injection (1, 6, or 30mg). After recruitment patients were stabilised on oral gabapentin for two weeks prior to implantation of the IT device. After patients had recovered from surgery, they were then randomised and administered study medication. Patients were then followed up for 22 days, at which time outcome data was collected. See Figure 2 for trial schedule.

The primary outcome of the trial was average daily NPRS, where 0 represented no pain and 10 represented worse possible pain. The difference between each patient's baseline and day-22 score was calculated to determine either improvement of worsening of pain. The investigators also assessed level of response; defined as 30 or 50% reduction in NPRS between baseline and day 22. Secondary efficacy measures included the Brief Pain Inventory, quality of life using the SF-36, the Beck Depression Inventory of emotional functioning and daily opioid use normalised to oral morphine equivalent doses. Adverse events associated with study drug and or infusion system were also captured.

Figure 2. Trial schedule (Rauck 2013)



Risk of Bias

This study had a low risk of bias. Patients were randomised according to a randomisation schedule prepared by a statistician who was not associated with the study. The study medication was prepared using coded syringe labels, which were stored in sealed sequentially numbered randomisation envelopes. Patients, investigators, site and sponsor staffs were all blinded to treatment.

The study was adequately powered to detect a clinically significant change from baseline of 2.5 points on the NPRS (p=0.05, 90% power). Of the 171 patients recruited, only a small number (2.9%) withdrew from the study and all outcomes were assessed using intention to treat analysis.

Results

Effectiveness

Changes in pain scores were not significantly different for any of the gabapentin doses compared with placebo (corresponding 95% CI for each dose compared with placebo: 1 mg/day -0.46 to 0.61; 6mg/day -0.17 to 0.92; 30mg/day -0.05 to 1.04).

No statistically significant difference between placebo and gabapentin groups was observed in the proportion of patients reaching either a 30 or 50% reduction on average daily NPRS. There was also no significant difference between placebo and gabapentin for secondary outcomes: Brief pain inventory; SF-36; Beck depression inventory of emotional functioning; and daily opioid use.

Adverse Events

The majority of patients (162/171, 94.7%) experienced one or more adverse events (AEs). In total, 721 AEs were reported. Twelve of 171 (12.9%) patients experienced serious AEs (specific events not reported but did not include death). Drug related AEs were observed in 71 of 171 patients (41.5%) and were similar to those commonly observed for oral gabapentin such as nausea, somnolence, headache, dizziness fatigue and peripheral oedema. Device-related AEs were observed in 77 of 171 (45%) patients; the most common of which were transient lumbar puncture headache and pain as a consequence of device implant surgery.

Contraindications

Contraindications were not reported.

Effect of Training

Effect of training was not reported.

Discussion

Intrathecal administration of gabapentin did not demonstrate statistically significant or clinically meaningful improvements in pain, function, quality of life or medication use when compared to placebo. The study did not measure the effect of gabapentin on return to work or healthcare utilisation.

The quality of evidence for gabapentin was judged as low due to concerns with imprecision secondary to small participant numbers (see Table 4.1.3 for GRADE evidence profile). As such, there is low quality evidence indicating IT gabapentin is no better than placebo in reducing pain and medication use or increasing function and quality of life in patients with persistent non-cancer pain. A number of drug-related adverse events and device-related adverse events were observed in nearly 95% of patients. With regards to future studies, the trial sponsor has no plans to conduct further studies on IT gabapentin.

Table 4.1.1. Key information from recent primary studies for other medications

Reference	Inclusion, exclusion criteria (for P.I.C.O)	Study design	Conclusion/recommendation
Eisenach (2010) Role of spinal cyclooxygenase in human postoperative and chronic pain	**Patient/population:** The publication contains information on three studies 1. an open label study of 15 patients on chronic IT morphine treated with 0.5– 2.0 mg of IT ketorolac 2. a double blind cross-over RCT of 12 patients on chronic IT morphine treated with IT saline or 2.0 mg of ketorolac 3. a double blind RCT of 30 patients undergoing total vaginal hysterectomy IT saline vs. 2.0 mg of ketorolac, with bupivacaine In this report, we describe only the second study (the cross-over RCT), as it fits the inclusion criteria. **Intervention:** Preservative-free ketorolac (2 mg) **Control:** IT saline **Outcomes assessed:** • Visual Analogue Scale (VAS) pain intensity after IT injection • Visual Analogue Scale (VAS) unpleasantness to thermal testing after IT injection	Crossover RCT	The results showed that both pain intensity and unpleasantness decreased with time after IT injections, but the reduction was not significantly different from placebo. Thus the author concluded that 'IT ketorolac did not relieve chronic pain or extend anesthesia or analgesia' (pg 1225).
Rauck (2013) Intrathecal gabapentin to treat chronic intractable noncancer pain	**Patient/population:** Patients with chronic pain eligible for IT drug therapy (n=170) **Intervention:** Study subjects were implanted with IT drug delivery system and then randomised to receive either 1, 6 or 30 mg/ day gabapentin (1mg gabapentin n=42; 6mg gabapentin n=41; 30 mg gabapentin n= 43) **Control:** Placebo (0.9% sodium chloride injection) administered using an IT drug delivery system n= 44 **Outcomes assessed:** • Change from baseline scores for: Numerical pain rating scale; Brief Pain inventory; SF-36 (quality of life); Beck Depression Inventory of emotional functioning; Daily opioid use • Responder level at least 30% and at least 50% reduction in NPRS between baseline and day 22 • Adverse events	RCT	Based on the results of a low quality study, IT administration of gabapentin did not demonstrate statistically significant or clinically meaningful improvements in pain outcomes when compared to placebo. Both the implantable device and gabapentin medication were associated with a number of adverse events.

Table 4.1.2 GRADE evidence profile for ketorolac

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketorolac	Placebo	Relative (95% CI)	Absolute	
Numerical pain rating scale (follow-up 22 days; measured with: 0-10 scale; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12 (crossover study)		Not estimable because data was given in graph format only		⊕OOO VERY LOW

[1] No reporting of allocation concealment
[2] Very small sample size (n=12)

Table 4.1.3 GRADE evidence profile for gabapentin

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IT gabapentin (30mg/day)	IT saline	Relative (95% CI)	Absolute	
Numerical pain rating scale (follow-up 22 days; measured with: 0-10 scale; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 0.05 higher (0.07 lower to 1.07 higher)	⊕⊕OO LOW
Brief pain inventory (follow-up 22 days; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 0.18 lower (0.89 lower to 0.53 higher)	⊕⊕OO LOW
SF-36: overall physical component (follow-up 22 days; Better indicated by higher values)											

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 0.30 higher (2.44 lower to 3.04 higher)	⊕⊕OO LOW
SF-36: overall mental outcome component (follow-up 22 days; Better indicated by higher values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 2.50 lower (6.81 lower to 1.81 higher)	⊕⊕OO LOW
Beck depression inventory (follow-up 22 days; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 0.70 higher (2.64 lower to 4.04 higher)	⊕⊕OO LOW
Daily opioid use (follow-up 22 days; measured with: mg/day; Better indicated by lower values)											
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[1,2]	none	41	43	-	MD 11.0 lower (27.84 lower to 5.64 higher)	⊕⊕OO LOW

[1] Small sample size (n=84)

[2] 95% confidence interval is wide and crosses the line of no effect

MD = mean difference

DISCUSSION & CONCLUSION

We searched for EBGs, SRs, HTAs, RCTs and CCTs that evaluated the effect of IT infusions for the treatment of persistent non-cancer pain. We sought to answer the following questions:

- In what conditions are IT infusions indicated?
- What is the effectiveness of IT infusions on persistent spinal pain in these conditions?
- What is the effect of IT infusions on function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation?
- In what patient groups/conditions are IT infusions contraindicated?
- What are the risks associated with use of IT infusions?
- What are the impact of training and/or experience of practitioners on patient outcomes?

The searches identified:

- 1 RCT and 1 EBG for the use of analgesics (opioids)
- 2 RCTs for the use of other medications (ketorolac and gabapentin)

A summary of the results for each question is provided below.

In what conditions are IT infusions indicated?

Based on the evidence, the indication for IT use is unclear. The patient groups recruited by the studies were broad, e.g. patients with chronic pain receiving IT morphine for at least 6 weeks (Eisenach 2010) or adults with non-cancer pain eligible for IT infusion (Rauk 2013, Raphael 2013). Furthermore, the majority of studies did not report the origin or type of pain experienced by the patients (e.g. in Manchikanti 2013). Predominantly, they were described as ‘patients with chronic non-cancer pain’ or ‘patients with chronic pain of nonmalignant etiology’.

What is the effectiveness of IT infusions on persistent pain and other patient relevant outcomes?

Analgesics (Opioids)

The results of studies assessing the effectiveness of opiods on pain and function were mixed. In addition, the quality of the evidence was rated as very low. As such, we are uncertain about the effect of analgesics (opioids) in patients with persistent non-cancer pain on pain and function. No studies were identified that measured other pre-specified outcomes (i.e. quality of life, return to work, medication use and healthcare utilisation).

Anti-spasmodic drugs (baclofen)

No primary or secondary research was identified about the effect of anti-spasmodic drugs in patients with persistent non-cancer pain. Therefore, the effectiveness of anti-spasmodic agents in the treatment of persistent pain is unclear.

Calcium-channel antagonists (ziconotide)
No primary or secondary research was identified about the effect of calcium-channel antagonists in patients with persistent non-cancer pain. Therefore, the effectiveness of calcium channel blockers in the treatment of persistent pain is unclear.

Other medications
Ketorolac
There is very low quality evidence indicating IT ketorolac is no better than placebo in reducing pain and medication use or increasing function and quality of life in patients with persistent non-cancer pain. Due to the very low quality of the evidence, we are therefore uncertain about the effect of ketorolac in patients with persistent non-cancer pain on pain. No studies were identified that measured other pre-specified outcomes (i.e. function (physical, psychological, social), quality of life, return to work, medication use and healthcare utilisation).

Gabapentin
There is low quality evidence indicating IT gabapentin is no better than placebo in reducing pain and medication use or increasing function and quality of life in patients with persistent non-cancer pain. No studies were identified that measured other pre-specified outcomes (i.e. return to work and healthcare utilisation).

In what patient groups/conditions are IT infusions contraindicated?
This was not reported by any of the included studies

What are the risks associated with use of IT infusions?
The risks identified for IT infusions include:

Analgesics (opioids)
While the vast majority of complications for IT opioid therapy were minor (such as catheter kinking, infection and nausea), some serious complications such as death (Coffey 2009) and granuloma formation (Miele 2006) were reported.

Anti- spasmodic drugs (baclofen)
No evidence was identified to allow an assessment of the risks associated with anti-spasmodic drugs.

Calcium-channel antagonists (ziconotide)
No evidence was identified to allow an assessment of the risks associated with calcium-channel antagonists.

Other medications

Ketorolac

The following symptoms were reported after injections: numbness in left leg for less than two hours, mild sedation, mild dizziness, hot sensation in the back, headache, urinary retention and hives. However, the incidence of adverse events did not differ between ketorolac and saline injection.

Gabapentin

No adverse events were reported that can definitely be related to gabapentin. A total of 121 adverse events were reported as being possibly and 9 adverse events as being probably related to gabapentin respectively. The most common drug related adverse events were nausea, somnolence, headache, dizziness, fatigue and peripheral edema.

What are the impact of training and/or experience of practitioners on patient outcomes?

The issue of training was not explored in any of the included studies.

DISCLAIMER

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and the National Trauma Research Institute do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and the National Trauma Research Institute cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors or omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

CONFLICT OF INTEREST

The TAC/WS Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/WS Health and Disability Strategy Group have engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

REFERENCES

1. Donoghue E, Piccenna L. Implantable pain therapies: Intrathecal infusions - Evidence Review. 2011:1-22.
2. Coffey R, Owens M, Broste S, Dubois M, Ferrante F, Schultz D, Stearns L, Turner M. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. Anesthesiology. 2009;111(4):881-91.
3. Miele V, Price K, Bloomfield S, Hogg J, Bailes J. A review of intrathecal morphine therapy related granulomas. European Journal of Pain. 2006;10(3):251-61.
4. Australian and New Zealand College of Anaesthetists. Guidelines for patient assessment and implantation of intrathecal catheters, ports and pumps for intrathecal therapy. 2005:1-5.
5. Australian and New Zealand College of Anaesthetists. Guidelines for longterm intrathecal infusions (analgesics / adjuvants / antispasmodics). 2013:1-5.
6. Eisenach J, Curry R, Rauck R, Pan P, Yaksh T. Role of spinal cyclooxygenase in human postoperative and chronic pain. Anesthesiology. 2010;112(5):1225-33.
7. Cheng J, Pan H, Eisenach J. Antiallodynic effect of intrathecal gabapentin and its interaction with clonidine in a rat model of postoperative pain. Anesthesiology. 2000;92(4):1126-31.
8. Kaneko M, Mestre C, Sanchez E, Hammond D. Intrathecally administered gabapentin inhibits formalin-evoked nociception and the expression of Fos-like immunoreactivity in the spinal cord of the rat. J Pharmacol Exp Ther. 2000;292(2):743-51.
9. Takeuchi Y, Takasu K, Honda M, Ono H, Tanabe M. Neurochemical evidence that supraspinally administered gabapentin activates the descending noradrenergic system after peripheral nerve injury. European Journal of Pharmacology. 2007;556(1-3):69-74.
10. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013: The GRADE Working Group; 2013. Available from: www.guidelinedevelopment.org/handbook.
11. Manchikanti L, Abdi S, Atluri S, Benyamin RM, Boswell MV, Buenaventura RM, Bryce DA, Burks PA, Caraway DL, Calodney AK, Cash KA, Christo PJ, Cohen SP, Colson J, Conn A, Cordner H, Coubarous S, Datta S, Deer TR, Diwan S, Falco FJE, Fellows B, Geffert S, Grider JS, Gupta S, Hameed H, Hameed M, Hansen H, Helm S, 2nd, Janata JW, Justiz R, Kaye AD, Lee M, Manchikanti KN, McManus CD, Onyewu O, Parr AT, Patel VB, Racz GB, Sehgal N, Sharma ML, Simopoulos TT, Singh V, Smith HS, Snook LT, Swicegood JR, Vallejo R, Ward SP, Wargo BW, Zhu J, Hirsch JA. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. Pain Physician. 2013;16(2 Suppl):S49-283.
12. Raphael J, Duarte R, Southall J, Nightingale P, Kitas G. Randomised, double-blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain. BMJ Open. 2013;3(7).
13. Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G, Fervers B, Graham I, Grimshaw J, Hanna S, Littlejohns P, Makarski J, Zitzelsberger L. AGREE II: advancing guideline development, reporting and evaluation in health care. Canadian Medical Association journal 2010;182(18):E839-42.
14. Coffey R, Owens M, Broste S, Dubois M, Ferrante F, Schultz D, Stearns L, Turner M. Medical practice perspective: identification and mitigation of risk factors for mortality associated with intrathecal opioids for non-cancer pain. Pain Medicine. 2010;11(7):1001-9.
15. Allen J, Horais K, Tozier N, Wegner K, Corbeil J, Mattrey R, Rossi S, Yaksh T. Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: a combined magnetic resonance imaging and histopathology investigation. Anesthesiology. 2006;105(3):581-9.

16. Coffey R, Burchiel K. Inflammatory mass lesions associated with intrathecal drug infusion catheters: report and observations on 41 patients. Neurosurgery. 2002;50(1):78-86; discussion -7.
17. Hooten W, Timming R, Belgrade M, Gaul J, Goertz M, Haake B, Myers C, Noonan M, Owens J, Saeger L, Schweim K, Shteyman G, Walker N. Assessment and management of chronic pain. Institute for Clinical Systems Improvement; 2013.
18. Accident Compensation Corporation. Interventional pain management 2005. Available from: http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/index.htm.
19. Jadad A, O'Brien M, Wingerchuk D, Angle P, Biagi H, Denkers M, Tamayo C, Gauld M. Management of Chronic Central Neuropathic Pain Following Traumatic Spinal Cord Injury: Summary. 2001 Sep. AHRQ Evidence Report Summaries. Rockville (MD): Agency for Healthcare Research and Quality (US); 2001.
20. Turner J, Sears J, Loeser J. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. The Clinical journal of pain. 2007;23(2):180-95.
21. Rauck R, Coffey R, Schultz D, Wallace M, Webster L, McCarville S, Grigsby E, Page L. Intrathecal gabapentin to treat chronic intractable noncancer pain. Anesthesiology. 2013;119(3):675-86.