Transport Accident Commission & WorkSafe Victoria

Evidence Service

Implantable pain therapies: Intrathecal (IT) infusions

Plain language summary

Treatments for persistent pain can involve many therapies including; medication, physiotherapy, psychological therapy and nerve blocks. In some patients these may not work or cause unpleasant side effects. For this small group of patients, drugs can be given by intrathecal infusion. A pump is placed under the skin usually around the stomach region. Tubes from the pump trickle out the drug into the space around the spinal cord. This may give the patient pain relief.

This review looked at whether IT infusions are helpful for persistent pain that is not due to cancer. The review did not find enough evidence to confirm that IT infusions are helpful for pain. There are also possible harms such as; side effects (e.g. nausea, dizziness, sleepiness, headache, addiction) and complications such as pump malfunction, misplacement and infection.

Accompanying documents to this report	
Title	*Report number*
Implantable pain therapies: Intrathecal (IT) infusions – Evidence Summary	Research Report No. *0611-002-R7.1*
Implantable pain therapies: Intrathecal (IT) infusions – Plain Language Summary	Research Report No. *0611-002-R7.2*
Implantable pain therapies: Intrathecal (IT) infusions – Technical Report	Research Report No. *0611-002-R7.3*

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Evidence summary

Overview

This evidence review is an update of a previous review requested by the Transport Accident Commission (TAC) and WorkSafe Victoria (WSV) conducted in September 2008.[1] The current report has identified further evidence for the effectiveness of IT opioids and IT ketorolac, a non-steroidal anti-inflammatory drug (NSAID). No new evidence for the effectiveness of IT baclofen and IT ziconotide was identified since the previous report.

At present, the evidence available for the effectiveness of intrathecal (IT) infusions in patients with persistent, non-cancer pain is insufficient (IT opioids, baclofen, ziconotide, and ketorolac).

Definition

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, intrathecal (IT) infusions may be an effective treatment. A pump is implanted under the skin usually in the abdominal region. Tubes from the implanted pump are programmed to trickle out the drug at a certain rate into the space around the spinal cord (intrathecal or IT) which may provide the patient with sufficient pain relief.

The following evidence review identified a total of fifteen studies (three evidence-based guidelines, three health technology assessments, eight systematic reviews and one randomised clinical trial) of IT infusions for persistent pain that met the selection criteria.

ANALGESICS (OPIOIDS):	The most recent high quality systematic review (SR)[2] was found to be well conducted. The included studies in the SR, which were case series (low level evidence), **provided limited evidence to determine whether IT opioids are effective for chronic, persistent non-cancer pain.**
ANTI-SPASMODICS (BACLOFEN):	Only low level evidence based on a single case series study[3, 4] exists for the effectiveness of IT baclofen in the treatment of persistent pain. Therefore, there is **insufficient evidence to determine whether IT baclofen is effective for chronic, persistent non-cancer pain.**
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	The most comprehensive, up-to-date high quality SR[5] identified, found that "no studies for ziconotide met the inclusion criteria for either effectiveness or complications". No further primary studies were identified according to the inclusion criteria requested in this report. Hence, there is **insufficient evidence to determine the benefits of IT ziconotide treatment for chronic, persistent non-cancer pain.**
OTHER MEDICATIONS (KETOROLAC):	A small cross-over RCT[6] did not find a statistically significant difference in treatment effect following IT ketorolac or placebo with established, simultaneous IT morphine,

	although a trend for reduced pain intensity and unpleasantness was present following IT ketorolac. Overall, this led us to conclude that **there is insufficient evidence of effectiveness of IT ketorolac on persistent pain.**

In what clinical conditions is this intervention indicated for use?

Drug infusions through implantable pumps are indicated and approved for use by the TGA for baclofen only. Morphine (opioids), ziconotide and other medications (ketorolac) are not approved and are prescribed by some physicians in an "off label" capacity. For "off label" use appropriate patient consent is required.

Findings in the following report identify the target group for use of IT infusions (opioids and ketorolac) to be adults with chronic non-cancer pain that have not experienced pain relief with conventional treatments. Insufficient evidence is available to confirm which patients IT baclofen and IT ziconotide can be used for.

What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?

ANALGESICS (OPIOIDS):	There is **insufficient evidence** to answer this question.
ANTI-SPASMODICS (BACLOFEN):	There is **insufficient evidence** to answer this question.
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	There is **no evidence** to answer this question.
OTHER MEDICATIONS (KETOROLAC):	There is **insufficient evidence** to answer this question.

What is the effect of this intervention on function, quality of life, return to work, medication use and use of the healthcare system?

ANALGESICS (OPIOIDS):	There is **insufficient evidence** to answer this question.
ANTI-SPASMODICS (BACLOFEN):	There is **insufficient evidence** to answer this question.
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	There is **no evidence** to answer this question.
OTHER MEDICATIONS (KETOROLAC):	There is **insufficient evidence** to answer this question.

In what patient groups/conditions is use of this intervention contraindicated?

Patient groups/conditions in which use of IT infusions are contraindicated are

- When infection is present[7]
- When the pump cannot be implanted 2.5 cm or less from the surface of the skin[7]
- When body size is not sufficient to accept pump bulk and weight[7]
- Allergy or hypersensitivity to the drug being used[7, 8]
- Blood thinning medications[9]
- In patients who have another implanted device, such as a pacemaker[8]

- Drugs with preservatives[7]
- Epilepsy refractory to therapy[8]
- Previous history of psychosis[9]

The Australian and New Zealand College of Anesthetists caution the use of IT therapy in patients where psychological factors are considered to be a major pain modifying factor. [10]

What are the risks associated with use of this intervention?

Device-related adverse events were only reported for IT opioids,[2] however the same device is utilised for all other IT drugs. Adverse events include pump and catheter malfunctions and malpositioning, surgical complications and postsurgical complications.

The following drug-related adverse events were reported with IT ketorolac[6] including mild sedation (n=2, lasting < 2 hours), mild dizziness (n=1, lasting < 30 minutes, and a hot sensation in the back, headache, urinary retention, and hives (n=1, lasting< 4 hours). Following saline infusion in the RCT, mild sedation (n=2, lasting < 1 hour, mild nausea (n=2, lasting < 1 hour), and mild headache (n=1, lasting < 2 hours) were reported.

The only serious adverse event reported following IT administration of opioids was hallucinations.[2]

As no evidence was available for IT baclofen or IT ziconotide, drug-related adverse events remain unknown.

Glossary of Findings	
Insufficient	Little or no evidence exists to answer this question
Limited evidence of effectiveness	There is some evidence of effectiveness but not enough to be sure. More high quality studies are needed before conclusions can be drawn.

Transport Accident Commission & WorkSafe Victoria

Evidence Service

Implantable pain therapies: Intrathecal infusions

Evidence Review

July 2011

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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 intrathecal (IT) infusions of analgesic, local anaesthetic, antispasmodic and other pharmacological agents. In order to develop and update policies for the use of IPTs in patients with persistent pain, the Health Services Group of the Transport Accident Commission and WorkSafe Victoria (TAC/WSV) requested an update of the Evidence Reviews of IPTs published in September 2008[1]. In light of the complexity of the research questions and the multiple sources of information available, the previous review developed two separate reports; one for implantable IT infusions and another for neurostimulation. This approach was continued for this update.

The focus of this review is to evaluate the effectiveness and safety of implantable IT infusions on 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, intrathecal (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 intrathecal space around the spine which contains cerebrospinal fluid that bathes the spinal cord, delivering medication to where it has its action, and 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.[10, 11] 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-spasmodics (baclofen),
- calcium channel blockers (ziconotide), and
- other medications (including ketorolac and midazolam)

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 TGA's "Access to Unapproved Therapeutic Goods" scheme.[10]

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 abundantly present in the central nervous system. Studies have found a large number of side effects associated with the use of opioids as well as complications when used in IT pumps. Some of these have severe consequences, however it is difficult to know from the information available how likely these problems are to occur.

Opioids used for IT treatment include morphine, hydromorphone, fentanyl, buprenorphine and sufentanil. These drugs have not been approved by the Australian Therapeutic Goods Administration (TGA) for IT use.

2. Anti-spasmodics (baclofen)

Baclofen is a GABA-β receptor agonist and is a medication 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 by binding to pre-synaptic GABA-β receptors, which in turn inhibits the release of neurotransmitter (GABA) onto neurons of the spinal cord that causes 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.

Baclofen is only approved by the TGA for IT use for spasticity. Lioresal® Intrathecal (baclofen injection) is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin that are unresponsive to orally administered antispasmodics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

3. Calcium channel blockers (ziconotide)

Ziconotide is the man-made 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 abundantly 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 (including ketorolac and midazolam)

There are other medications which have been given intrathecally via a pump. 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.[6] The drug was initially administered systemically as a potent pain relief agent in 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 an early open-label study, IT ketorolac did not reduce pain from applying heat stimuli to the skin, although no serious adverse events were reported.[6]

Ketorolac has not been approved by the TGA for IT use.

Other medications have been used intrathecally for the treatment of chronic, severe pain. These include clonidine, bupivacaine, sufentanil, fentanyl, midazolam and gabapentin. However, most of these drugs have only shown effectiveness in the treatment of pain in pre-clinical studies and hence are not approved by the TGA for IT use.

QUESTIONS

This Evidence Review sought to find the most up-to-date, high quality source of evidence to answer the following questions regarding IT drug infusions in persistent pain due to work-related or transport accident injuries:

- In what clinical conditions is this intervention indicated?
- What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?
- What is the effect of this intervention on function (physical, psychological, social), quality of life, return to work, medication use and use of the healthcare system?
- In what patient groups/conditions is this intervention contraindicated?
- What are the risks associated with use of this intervention?

METHODS

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

A comprehensive search of Medline, Embase and the Cochrane Library, was undertaken in March 2011 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)), and any relevant randomised controlled trials (RCTs) and controlled clinical trials (CCTs). Inclusion and exclusion criteria were established *a priori*. A comprehensive search of the internet, relevant websites and electronic health databases was also undertaken (see Appendix 2, Tables A2.2-A2.4 for search details). 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). Synthesised evidence (EBGs, SRs and HTAs) that met the selection criteria was reviewed to identify the most up-to-date and comprehensive source. This evidence was then critically appraised to determine whether it was of high quality. This process was repeated for additional sources of evidence, until the most recent, comprehensive and high quality source of evidence was identified. Final source documents were compared to other evidence sources for consistency of findings and included studies. The available synthesised evidence was mapped (see Table 2), and the algorithm in Table 1 was followed to determine the next steps necessary to answer the clinical questions.

Table 1. Further action required to answer clinical questions

Is there any synthesised research available? (e.g. EBGs, HTAs, SRs)				
Yes			No	
Is this good quality research?			Are RCTs available?	
Yes		No	Yes	No
Is it current (within 2 years)?				
Yes	No			
No further action	Update existing SR	Undertake new SR	Undertake new SR	Consider looking for lower levels of evidence

Data on characteristics of all included studies were extracted and summarised (see Appendix 4). The most recent, relevant, high quality systematic review was used to address the questions posed above.

RESULTS

An initial search of electronic databases yielded 4141 articles. After reviewing the title, abstract or full text, one EBG,[12] two HTAs,[13, 14] nine SRs[2, 5, 13-19] and three RCTs,[6, 20, 21] were found that met the selection criteria. Internet searches yielded two additional EBGs,[4, 22] one HTA[3] and one additional SR.[23] In the process of critically appraising these studies, two SRs and two RCTs were excluded.

In total 15 studies (three EBGs, three HTAs, eight SRs and one RCT) of IT infusions for persistent pain (published between 1996 and 2011) met our selection criteria (see Table 2 for number of studies and Appendix 2 Table A2.1 for selection criteria). A list and summary of included studies can be found in Appendices 3 and 4, respectively.

Table 2. Evidence map of included studies by study-type

	Synthesised Studies		Primary studies	TOTAL
Drug category	EBGs*	SRs & HTAs*		
Opioids	2 EBGs	9 SRs	-	11
Baclofen	1 EBG	2 SR/HTA	-	3
Ziconotide	-	1 SR	-	1
Other medications	1 EBG	-	1 RCT	1

**columns may not add up to totals as some systematic review (SRs) and primary studies (RCTs) identified evaluated IT infusions in more than one drug category.*

Results are reported in more detail below by drug category.

1. ANALGESICS (opioids)

Evidence identified

Searches yielded a total of 11 studies of IT opioids for the treatment of persistent pain published between 1996 and 2011. The number of studies by study design is illustrated in Table 2 above. A summary of these studies can be found in Appendix 4, Table 4.1.

The effectiveness of IT opioids on persistent pain has been assessed in numerous synthesised studies. Three SRs were recently identified as potentially relevant.[2, 15, 23] One of these SRs[15] included a study[24] that combined results for cancer and non-cancer pain patients. Our review was limited to patients with persistent pain not due to cancer and so this SR was excluded from the analysis.

Two of the most up-to-date SRs were critically appraised (see Appendix 5). It was decided that Noble, M et al[2] would be used as the primary reference as it contained a larger number of studies which were more recent and also assessed long-term functional outcomes including quality of life (QoL) and functional levels which were questions needing to be answered for the evidence review.

Table 3. Key information from most recent, comprehensive, high quality systematic review *(Noble, M et al, 2010)* - OPIOIDS

Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. [Meta-Analysis Review]. 2010(1):CD006605.	
Study design	Systematic review
Scope	**Patient/population:** n = 231 (10 case series) **Conditions indicated for use:** Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least three months **Intervention:** IT morphine, IT sufentanil citrate, IT methadone, morphine clorhidrate or tramadol, IT morphine with bupivacaine and/or clonidine and/or midazolam, IT dilaudid, IT fentanyl and IT baclofen (see Appendix 4 for further details) **Outcomes assessed:** "We assessed adverse events (side effects), discontinuation from study due to adverse events, discontinuation from study due to insufficient pain relief, average change in pain score, proportion of patients with at least 50% pain relief, health-related quality of life, and function".
Efficacy and effectiveness of IT drug infusion for persistent pain	**Average change in pain scores, as assessed by visual analogue scale (VAS) (n = 220)** Before treatment commenced, the VAS scores of the included studies were combined, giving a score of 8.70 out of 10 (95% CI: 8.37 to 9.04), indicating severe pain. After treatment, this pooled VAS score was reduced to 4.45 out of 10 (95% CI: 3.44 to 5.47), indicating moderate pain. **Pts with at least 50% pain relief (n = 151)** The summarized proportion of participants (from combined included studies) who had at least a 50% reduction in pain was 44.5% (95% CI: 27.2% to 63.2%).
Effect of IT drug infusion on function, quality of life, return to work, medication use and use of the healthcare system?	**Quality of life (QoL) (n = 92)** Each study used a different instrument to assess quality of life (QoL). One of the studies had inconclusive findings,[25] one reported a small benefit,[26] and one reported a large benefit.[27] The overall effect size (or standardized mean difference, SMD) following

	statistical analysis revealed no significant improvement in quality of life after administration of IT opioids 1.02 (95% CI -0.04 to 2.09). **Function Levels (n = 98)** Each study used a different instrument to assess function. Study findings were inconsistent, with one study showing inconclusive findings,[28] another showing a moderate difference (effect size),[26] and another a large difference (effect size).[29] Following statistical analysis, all the studies showed that there was no significant improvement in functional levels after administration of IT opioid (SMD 0.56, 95% CI -0.02 to 1.13). These results however are limited by the high heterogeneity between studies.
Which patient groups/ conditions is use of IT drug infusion contraindicated?	Not reported
Risks associated with use of IT drug infusion	**Adverse Events (AEs) (n = 228, 10 studies)** Pump and catheter malfunctions and malpositioning, surgical complications, and postsurgical complications were reported. The percentage of participants whose device complications required reoperation was quite high in some studies (20-27%). Two studies reported a total of six deaths, due to chronic obstructive pulmonary disease, pericolonic abscess, and myocardial infarction (n=2), suicide, and an unknown cause (n = 1). The SR did not report if these events were due to the drug or the implantable pump itself. **Discontinuation from study due to AEs (n = 86)** Following pooled analysis of all included studies it was estimated that 8.9% of patients discontinued the study due to adverse events, however this result was not statistically significant. **Discontinuation from study due to insufficient pain relief (n = 113)** The summary rate of discontinuation due to insufficient pain relief was 7.6% (95% CI: 3.7% to 14.8%).
Conclusion/ Recommendation	"Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare."
Recommendation category	Insufficient evidence
Quality assessment results	This SR was well conducted and considered to have a low risk of bias (see Appendix 5 for quality appraisal)
Our comments/summary	Although this SR was well conducted it included nine observational studies that assessed IT opioids for persistent pain. The authors conclude that there is only weak evidence of therapeutic effectiveness of IT opioids for persistent pain,

	and insufficient evidence for health-related quality of life outcomes.

Findings

Due to a lack of high quality primary studies (i.e. RCTs), there is **insufficient evidence** to determine the effectiveness of IT opioids for the treatment of persistent pain.

2. ANTI-SPASMODICS (baclofen)

Evidence identified

Searches yielded one EBG, one HTA and one SR for IT baclofen for the treatment of persistent pain (published between 1996 and 2011). The HTA[4] and SR[3] were critically appraised (see Appendix 4) and it was discovered that both reviews were non-systematic literature reviews, a study type excluded in the selection criteria of this evidence review (see Appendix 5) and hence they were excluded. The number of included studies by study design is illustrated in Table 2. A summary of these studies can be found in Appendix 4, Table 4.1.

The EBG was appraised and found to be well conducted with a low risk of bias. However, it did not identify any controlled studies that met the inclusion/exclusion criteria for this report.

In summary, there is **insufficient** evidence to know whether IT baclofen is useful.

3. CALCIUM CHANNEL BLOCKERS (ziconotide)

Evidence identified

Searches yielded one SR for IT ziconotide for the treatment of persistent pain. The SR[5] was appraised and found to be well conducted with a low risk of bias. Details of the appraisal are in Appendix 5.

The authors of the SR found that *"no studies for ziconotide met the inclusion criteria for either effectiveness or the complications review"*.

4. OTHER MEDICATIONS (ketorolac)

Evidence identified

Searches yielded a total of 2 studies (1 EBG and 1 Randomised Cross Over Trial) for other IT medications for the treatment of persistent pain published between 1996 and 2011. The number of studies by study design is illustrated in Table 2. A summary of these studies can be found in Appendix 4, Table 4.1.

The EBG[22] was appraised and found to be of low quality with a potentially high risk of bias. It included a section on IT medication delivery systems, however it did not indicate the patient group (condition or age), the drug used or the outcomes reported. We chose to use the most-up-to-date, high quality evidence which was a randomised cross over trial by Eisenach[6] as the basis of this section of the report.

This cross-over trial randomised patients with chronic pain already receiving IT morphine for 6 weeks to receive preservative free ketorolac, 2mg, or placebo (saline) on their first visit, with the alternative treatment on their second visit. Patients returned after at least one week, but no more than 3 months later, for the crossover treatment. This study reported no significant difference in

pain intensity and unpleasantness between ketorolac and placebo. There was also no difference in the incidence of adverse events between groups.

These results however, are limited by small sample size and the amount and timing of ketorolac dosing. Furthermore it is unclear whether the results were subject to carryover effects between the treatment phases as a wash out period was not reported. The generalisability of the results is also unclear as the authors state "That the paper was more fundamental than practical, since there no longer exists a preservative free solution of ketorolac for spinal administration" (personal correspondence).

Table 5. Key information from most recent, comprehensive, high quality primary study *(Eisenach 2010)* – OTHER MEDICATIONS (IT ketorolac)

Eisenach, J.C., et al., Role of spinal cyclooxygenase in human postoperative and chronic pain. Anesthesiology, 2010. 112(5): p. 1225-33.	
Study design	Randomised cross-over trial
Scope	**Patient/population:** n=12 **Conditions indicated for use:** Patients with chronic pain, already receiving IT morphine for at least 6 weeks **Intervention:** IT morphine (mean 9.8mg; range 1.3 – 50mg/day) with IT ketorolac (2.0mg) **Comparator**: Saline + IT morphine (mean 9.8mg; range 1.3 – 50mg/day) **Outcomes assessed:** Pain intensity (pain score and ≥30% or 50% pain relief), unpleasantness and adverse events
Efficacy and effectiveness of IT drug infusion for persistent pain	"Both pain intensity (P = 0.01) and unpleasantness (P = 0.02) decreased with time after intrathecal injections, but there was no difference between ketorolac and saline, and there was no significant interaction between treatment and time."
Effect of IT drug infusion on function, quality of life, return to work, medication use and use of the healthcare system?	Not reported
Which patient groups/conditions is use of IT drug infusion contraindicated?	Patients allergic to ketorolac or morphine Pregnant women
Risks associated with use of IT drug infusion	No significant difference in the occurrence of adverse events was reported between ketorolac and placebo. Following IT ketorolac adverse events included mild sedation lasting < 2 hours (n = 2), mild dizziness lasting < 2 hours (n = 1), hot sensation in the back, headache, urinary retention and hives (n = 1) 4 days after injection, lasting < 4 hours. Following IT saline adverse events included mild sedation lasting < 1 hr

	(n = 2), mild nausea lasting < 1 hr (n = 2), mild headache lasting < 2 hr (n = 1). Two serious adverse events occurred. One patient experienced a numb left leg for less than 2 h after intrathecal injection of saline, and, as noted, this subject's pump contained bupivacaine. One patient committed suicide 6 months after study.
Conclusion/ Recommendation	"We failed to observe greater analgesia from intrathecal ketorolac than saline placebo in patients with primarily low back and lower extremity pain and a combination of somatic and neuropathic components". "2 mg of intrathecal ketorolac was not associated with serious side effects, failed to reduce ongoing pain in chronic pain patients more than placebo….These observations are limited by the small number of subjects studied, and patient population, and the amount and timing of ketorolac dosing." "Under the conditions of these studies, it seems that spinal cylcooxygenase activity does not contribute to chronic…pain."
Recommendation category	Insufficient evidence
Quality assessment results	The overall risk of bias was low-moderate with the authors not reporting on the allocation concealment, degree of error in group results and longer term treatment.
Our comments/summary	The authors were contacted regarding key methodological aspects which were not reported in paper. This included whether the groups were treated the same, if outcome measures were assessed independently and if the outcome assessors were blind to the intervention group. The authors stated that all of these were met. Patients were studied twice (cross-over study), hence they received placebo and ketorolac but at two alternative visits. A cross-over period of at least 1 week but no greater than 3 months was reported, suggesting some assurance of no direct placebo-ketorolac interactions which would modify the result (true effect size). However, it is unknown if the initial pain intensity and symptoms returned to test the efficacy of the second drug treatment, either saline or ketorolac. The study does not report the origin or type of pain patients enrolled in the RCT experienced, i.e. neuropathic or CRPS etc. This might have an impact on the response to pain reduction. Although the sample size for the RCT was only 12 patients, the authors of the study had justified this size well before conducting the study. Overall the study revealed no greater pain relief with IT ketorolac and IT morphine in comparison to IT morphine and saline (control).

Findings

Based on the findings of one cross-over trial there is **insufficient evidence** to determine whether IT ketorolac is effective in reducing chronic pain.

DISCUSSION & CONCLUSION

As a number of evidence syntheses assessing the effectiveness of IT infusion for chronic, persistent pain were identified, a pragmatic yet rigorous approach was taken whereby the best quality, most up-to-date source of evidence for each drug category was used to answer the review questions.

For all drug categories there is insufficient evidence to determine whether IT infusion is effective in relieving persistent pain and improving functional outcomes and quality of life in non-cancer patients. Although a number of well conducted SRs were identified, the evidence base of these was poor as the included studies were case series. Furthermore individual studies had no control groups and small sample sizes. The results of case series are difficult to interpret as influences of regression to the mean and selection bias cannot be ruled out. Furthermore the lack of a control group has the potential to obscure a relationship between treatment and outcome or suggest an association where one does not exist.

More studies are required to assess the risks associated with IT infusion. Only one systematic review reported on adverse events associated with the pump/device.[2] These included pump and catheter malfunctions and malpositioning, surgical complications, and postsurgical complications. Drug-related adverse events associated with the use of IT morphine, baclofen, ziconotide, and ketorolac alone were not reported by the primary studies. Only the randomised cross-over trial comparing morphine/ketorolac and morphine/saline combination therapy reported drug-related adverse events [6]. Although no significant difference was observed between groups, mild sedation and headache were the most commonly occurring adverse effects.

Based on the evidence, the indication for IT use is unclear. The patient groups recruited by the studies were broad, e.g. adults with non cancer pain of three months duration,[2] patients with persistent pain[3] or patients with chronic pain receiving IT morphine for at least 6 weeks.[6] Furthermore, none of the studies reported the origin or type of pain experienced by the patients.

Currently there is limited evidence to assess the efficacy of IT therapy for persistent non-cancer pain. Further studies are needed to address long term effectiveness and safety of IT agents both alone and in combination and assess in which population these are most suitable.

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/WSV 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/WSV Health Services Group has 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.

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Transport Accident Commission & WorkSafe Victoria

Evidence Service

Implantable pain therapies: Intrathecal infusions

Technical Report: Appendices 1-5

July 2011

Loretta Piccenna, Emma Donoghue

Report number: *0611-002-R7.3*

Accompanying documents to this report	
Title	*Report number*
Implantable pain therapies: Intrathecal (IT) infusions – Full Report	Research Report No. *0611-002-R7*
Implantable pain therapies: Intrathecal (IT) infusions – Evidence Summary	Research Report No. *0611-002-R7.1*
Implantable pain therapies: Intrathecal (IT) infusions – Plain Language Summary	Research Report No. *0611-002-R7.2*

A joint initiative of

INTRODUCTION

This technical report is a companion document to "Implantable Pain therapies: Intrathecal infusions Evidence Review". It contains detailed information about the methods used in the development of the Evidence Review, summaries of the studies included in the review, and quality appraisal results for the most recent and/or most relevant included studies.

CONTENTS

APPENDIX 1: REVIEW PROCESS

A two-staged approach was undertaken.

STAGE 1

Identify evidence available for each intervention

• Run search in health databases, websites and on the internet, limit to EBGs, HTAs, SRs, RCTs and controlled clinical trials (CCTs)

• Apply inclusion and exclusion criteria

Critically appraise synthesised research

• Start with most recent review, apply standard appraisal criteria

• If found to be of high quality, cross check to ensure references from all other synthesised research are included and check for consistency of findings

• If not high quality, appraise next most recent and repeat process

• If there are inconsistent findings across the existing reviews, investigate the possibility of synthesis of this information or whether a new systematic review is required

Decide on actions for Stage 2

• Map available evidence (as per Table A1.1)

• Identify whether sufficient high level evidence exists to answer questions or identify what further action needs to be taken (see algorithm in Table A1.2).

STAGE 2

Address further actions identified.

Table A1.1. Map of available evidence

	Synthesised Studies		Primary studies	TOTAL
Medication	EBGs	SRs & HTAs		
Analgesics (opioids - morphine, fentanyl etc.)				
Anti-spasmodics (baclofen)				
Calcium channel blockers (ziconotide)				
Other medications (including ketorolac and midazolam)				

Table A1.2. Further action required to answer clinical questions

<table>
<tr><td colspan="5">Is there any synthesised research available? (e.g. EBGs, HTAs, SRs)</td></tr>
<tr><td colspan="3">Yes</td><td colspan="2">No</td></tr>
<tr><td colspan="3">Is this good quality research?</td><td colspan="2">Are RCTs available?</td></tr>
<tr><td colspan="2">Yes</td><td>No</td><td>Yes</td><td>No</td></tr>
<tr><td colspan="2">Is it current (within 2 years)?</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td>No further action</td><td>Update existing SR</td><td>Undertake new SR</td><td>Undertake new SR</td><td>Consider looking for lower levels of evidence</td></tr>
</table>

APPENDIX 2: METHODS

TAC/WSV staff assisted in the development of search terms and inclusion and exclusion.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were established *a priori* (Table A2.1). References for primary screening were conducted by one reviewer. Ten percent of the references were screened by both reviewers independently to check for consistency of inclusion/exclusion decisions, and results were found to be 100% in agreement.

Table A2.1 Inclusion and Exclusion criteria

Patient/ population	**Inclusion:** Any individual with persistent pain (as defined in the study) • All ages • All genders
	Exclusion: • Acute pain (e.g. post-operative pain, women in labour) • Non-persistent pain (e.g. dysmenorrhoea) • Persistent pain due to systemic inflammatory conditions, vascular insufficiency, haematological disorders or cancer
Intervention/ indicator	**Inclusion:** Pharmacological agents administered at any stage of the management of persistent pain through intrathecal infusions (i.e. first-line, second-line, when all else fails or as an adjunct to therapy) • Analgesics (e.g. opioids - morphine) • Anti-spasmodics (e.g. baclofen) • Local anaesthetics • Other pain modifying agents used (e.g. clonidine, ziconotide)
	Exclusion: Drugs administered by routes other than intrathecal infusion (i.e. epidural, intravenous etc.)
Comparison/ control	**Inclusion:** Placebo, standard treatment or another implantable pain therapy
	Exclusion: Nil
Outcomes	**Inclusion:** Any (e.g. pain measures – scales, scores etc., physical function – mobility, disability, psychological – depression, social functioning/roles, activities of daily living , quality of life (QOL), return to work, medication use and healthcare utilisation)
	Exclusion: Nil
Setting	**Inclusion:** Any healthcare setting (e.g. acute, subacute, rehabilitation, community)
	Exclusion: Nil
Study Design	**Inclusion:** Evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs), randomised controlled trials (RCTs) and controlled clinical trials (CCTs)
	Exclusion: Non-evidence-based guidelines (EBGs), non-systematic reviews (SRs), cohort studies, case-control studies, case series, editorials, letters or commentaries
Publication details	**Inclusion:** Studies in English and conducted on humans
	Exclusion: Studies in languages other than English and/or conducted on animals
Time period	**Inclusion:** Any publication date
	Exclusion: Nil

Search methods

Searches were conducted in electronic health databases, relevant websites and the internet and were repeated from those performed in the initial 2008 evaluation.

Search strategies in electronic databases

It is difficult to ensure a comprehensive, up-to-date systematic search given the vast number of analgesic drugs available, the variety of generic terms used in different countries and the change in brand names over time. Hence drug terms were not included, however all relevant studies should be identified by combining terms related to chronic pain with terms related to the applicable routes of administration for intrathecal infusions. No terms have been included for comparison or outcomes to enable a broader search.

Internet searches to identify relevant websites

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice and Australian government health services known to contain evidence-based resources. Additional websites of specific relevance (e.g. accident compensation groups) were sought via an internet search using the Google 'Advanced Search' function. The term 'evidence' was combined with the terms 'accident', 'injury', 'trauma', 'road', 'transport', 'traffic', 'work', 'employment' and 'safety'.

Fourteen websites relevant to Implantable Pain Therapies were identified. These, and the 31 generic websites previously identified by the review team (9 professional organisations, 9 guideline services, 12 Australian government websites and 1 centre of evidence-based practice) were searched for relevant guidelines. The searches are outlined in detail in Table A2.4.

Website searches to identify relevant EBGs

Websites were searched using any lists of guidelines, publications or other resources identified on the site and scanned for relevant documents for both neurostimulation and intrathecal infusion. Where an internal search engine was available websites were searched using appropriate search strings relating to pain and the method of drug delivery.

Internet searches to identify relevant references

An internet search strategy was conducted using the Google 'Advanced Search' function. The search strings were limited to documents in English and were used to identify guidelines for both interventions

- pain AND (evidence OR guideline) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable)
- pain AND (evidence OR systematic OR review) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable)'

The searches are outlined in detail in Table A2.4.

The first 100 Google search results were screened and yielded no new studies. As Google search results are presented in order of relevance, we did not screen further.

Searches of reference lists

The reference lists of EBGs and SRs were also checked to identify any other potentially relevant EBGs, SRs or CCTs that had not been identified in our electronic searches.

Databases accessed

Table A2.2 Databases accessed

Evidence Source	Period	Date of Search	# hits
Medline (Ovid)	Ovid MEDLINE(R) 1948 to March Week 2 2011	17th March 2011	267
PreMedline (Ovid)	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 16, 2011	17th March 2011	0
All EBM (Ovid) *	Various	17th March 2011	21
CINAHL (Ovid)	1982 – May Week 1 2008	17th March 2011	733
EMBASE	EMBASE 1996 to 2011 Week 10	17th March 2011	553

*including The Cochrane Database of Systematic Reviews, DARE, CENTRAL, NHSEED, HTA and ACP Journal Club

Table A2.3 Major medical database search strategies

1	pain.ti,ab.	21	intra-thecal*.ti,ab.
2	exp Pain/	22	intraspinal*.ti,ab.
3	or/1-2	23	intra-spinal*.ti,ab.
4	persist*.ti,ab.	24	subarachnoid.ti,ab.
5	chronic.ti,ab.	25	sub-arachnoid.ti,ab.
6	long-term.ti,ab.	26	subdural*.ti,ab.
7	long term.ti,ab.	27	sub-dural*.ti,ab.
8	refractory.ti,ab.	28	or/14-27
9	intractable.ti,ab.	29	infus*.ti,ab.
10	or/4-9	30	pump*.ti,ab.
11	3 and 10	31	device*.ti,ab.
12	Pain, Intractable/	32	30 or 31
13	or/11-12	33	29 and 32
14	Infusion Pumps, Implantable/	34	spinal*.ti,ab.
15	Drug delivery systems/	35	infus*.ti,ab.
16	idds.ti,ab.	36	and/34-35
17	iip*.ti,ab.	37	or/28,33,36
18	synchromed.ti,ab.	38	and/13,37
19	medtronic.ti,ab.	39	limit 38 to (english language and humans)
20	intrathecal*.ti,ab.	40	limit 39 to ed="20080520 - 20110331"

* Search undertaken in Medline, adapted for use in other databases

Table A2.4 Website searches to identify relevant EBGs

Search 1: Identification of relevant guidelines for intrathecal implantable therapies using specific guideline-related websites		
Guideline Services	**Results**	**Search**
National Health and Medical Research Council (NHMRC)	Acute pain management: scientific evidence.2010 http://www.nhmrc.gov.au/publications/synopses/cp104syn.htm	Web page reviewed by: Health Guidelines
National Institute for Health and Clinical Excellence UK (NICE)	Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin http://guidance.nice.org.uk/TA159 Stereotactic radiosurgery for trigeminal neuralgia using the gamma knife http://guidance.nice.org.uk/IPG85	Web page reviewed by: published clinical guidelines, published interventional procedures Additional search by terms: chronic pain, intrathecal infusion, neurostimulation
New Zealand Guideline Group (NZGG)	N/A	Web page reviewed by: Guidelines Additional search by terms: pain, intrathecal infusion, neurostimulation
Scottish Intercollegiate Guidelines Network (SIGN)	N/A	Web page reviewed by: guidelines by subject Additional search by terms: chronic pain, intrathecal infusion, neurostimulation
Joanna Briggs Institute	N/A	Web page reviewed by: chronic pain, intrathecal infusion, neurostimulation
Guidelines International Network	• EFNS guidelines on neurostimulation therapy for neuropathic pain. European Federation of Neurological Societies. NGC:005909 http://www.guideline.gov/content.aspx?id=11372 • Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. American Society of Interventional Pain Physicians. NGC:007428	Web page reviewed by: pain AND spinal, chronic pain, intrathecal, neurostimulation

	• Spinal implants: DR8 pedicle screw system (Technology Review) • Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (TA159) • Khan kinetic treatment™ (KKT) (Technology Review) • Lumbosacraal radiculair syndroom (M55) • Epidurale Rückenmarkstimulation zur Therapie chronischer Schmerzen. S3-LL (DGAI/DGK/DGNC/DGN/DGSS) • Durerea lombara joasa. Ghid pentru medicul de familie • Percutaneous intradiscal laser ablation in the lumbar spine (IPG357) • International guideline library update	
Guidelines Advisory Committee	N/A	Web page reviewed by: GAC Endorsed Guidelines
National Guideline Clearinghouse US (NGC)	Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 2008 Oct. NGC:006752 National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]. EXPERT COMMENTARY Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. *What's New? What's Different?* Best practices & practice guidelines. 2008. NGC:007125 International Chiropractors Association - Medical Specialty Society.	Searched by: (1) pain AND (intrathecal* OR intra-thecal* OR intraspinal* OR intra-spinal* OR spinal* OR subarachnoid OR sub-arachnoid OR subdural* OR sub-dural*) (2) pain AND (stimulation OR electrode OR implantable)

	Chronic pain. 2008. NGC:007160 American College of Occupational and Environmental Medicine - Medical Specialty Society. Pain (chronic). 2003 (revised 2008 May 19). NGC:006564 Work Loss Data Institute - Public For Profit Organization. EFNS guidelines on neurostimulation therapy for neuropathic pain. 2007 Sep. NGC:005909 European Federation of Neurological Societies - Medical Specialty Society. Diagnosis and treatment of degenerative lumbar spinal stenosis. 2002 (revised 2007 Jan). NGC:005896 North American Spine Society - Medical Specialty Society. EFNS guidelines on pharmacological treatment of neuropathic pain. 2006 Nov. NGC:005495 European Federation of Neurological Societies - Medical Specialty Society. Practice guidelines for chronic pain management. An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. 1997 Apr (revised 2010 Apr). NGC:007951	

	American Society of Anesthesiologists - Medical Specialty Society. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. 2010 Jan. NGC:007678 American Academy of Neurology - Medical Specialty Society.	
TRIP Database searched on 15/3/2011 – 144 results total 144 searched on 19/5/2008 – 1986 results total 89	www.tripdatabase.com Relevant publications downloaded to Endnote library	Searched by: (1) pain AND (intrathecal* OR intra-thecal* OR intraspinal* OR intra-spinal* OR spinal* OR subarachnoid OR sub-arachnoid OR subdural* OR sub-dural*) Limited by: Guidelines) from:2008 to:2011 (2) pain AND (stimulation OR electrode OR implantable) Limited by: Guidelines from:2008 to:2011
Australian Government Websites containing Guidelines		
Australian Government Department of Health & Ageing	www.health.gov.au N/A	Scanned list of Topics for 'Pain'
Australian Institute of Health and Welfare	www.aihw.gov.au N/A	Web page reviewed by: Publications – searched within for guidelines uses Google to search

Health Insite	www.healthinsite.gov.au N/A	Web page reviewed by: Health topics – chronic pain – no guidelines locates SRs from the Cochrane Library
ACT Health	www.health.act.gov.au N/A	No EBGs
NSW Health	www.health.nsw.gov.au N/A	Only contains a small list of Paediatric Guidelines
NT Department of Health and Community Services	www.nt.gov.au/health N/A	No EBGs
Queensland Health	www.health.qld.gov.au N/A	No EBGs
SA Department of Health and Human Services	www.health.sa.gov.au N/A	+guideline +pain
Tasmanian Department of Health and Human Services	www.dhhs.tas.gov.au N/A	guideline AND pain
Victorian Department of Human Services	www.dhs.vic.gov.au N/A	guideline AND pain
Victorian Government Health Information	www.health.vic.gov.au N/A	List of topics: Pain, Chronic Pain
WA Department of Health	www.health.wa.gov.au N/A	guideline AND intrathecal AND pain neurostimulation

Centres of Evidence Based Practice Websites		
WA Centre for Evidence-based Nursing and Midwifery	http://wacebnm.curtin.edu.au N/A	Web page reviewed by: Resources – 'Reports, Guidelines and Article' (not relevant)
Other Accident Commissions		
Transport Accident Commission	www.tac.vic.gov.au/ N/A	Search for Guidance, Guideline
Australian Transport Safety Bureau	http://www.atsb.gov.au/ N/A	Search for Guideline
Road Safety Victoria (TAC)	www.tacsafety.com.au/	Search for Guideline
WorkSafe Victoria	http://www.workcover.vic.gov.au/ Evidence reviews • Implantable Pain Therapy Policy • Microsoft Word - Neurostimulation 20100430.doc	Search for intrathecal AND pain, neurostimulation No Guidelines – in publications contains guidance materials but not evidence-based (included for interest)
Traffic Injury Research Foundation	http://www.trafficinjuryresearch.com/index.cfm	No Guidelines – contains traffic reports
Motor Accidents Authority NSW	http://www.maa.nsw.gov.au/ N/A	Intrathecal AND pain, neurostimulation
WorkSafe British Columbia	http://www.worksafebc.com/ • Intrathecal Fentanyl Use In Patients With Chronic Nonmalignant Pain • Chronic Pain Treatments: What is the Evidence? • The effectiveness of spinal cord stimulator in treating complex	Intrathecal AND pain, neurostimulation

	regional pain ...	
Accident Compensation Corporation	http://www.acc.co.nz/index.htm *ACC2404 Traumatic brain injury guidelines* (2.488 MB) *Evidence tables: Infusion: Intrathecal Opioids* (295 KB) *Considered Judgement Form: Intrathecal Infusion of Baclofen* (61 KB) *Considered Judgement Form: Infusion - Intrathecal Baclofen* (42 KB) *Evidence tables: Infusion: Intrathecal Baclofen* (74 KB) *Evidence Based Review: Continuous Intrathecal Baclofen for Spasticity Management* (98 KB) *Intrathecal baclofen* *Evidence tables: Neuromodulation - Deep brain stimulation* (75 KB)	Intrathecal AND pain AND guideline
Pain Treatment Topics	http://pain-topics.org/guidelines_reports/index.php Pain Treatment Guidelines - Descriptions	(Intrathecal OR neurostimulation)Guideline

The George Institute	http://www.thegeorgeinstitute.org/iih/research/critical-care-&-trauma/critical-care-&-trauma_home.cfm http://www.tac.vic.gov.au/upload/Neurostimulation - full report.pdf http://www.tac.vic.gov.au/upload/Intrathecal infusion - full report.pdf	Intrathecal AND pain, neurostimulation
Injury Research and Prevention Unit	http://www.injuryresearch.bc.ca/ N/A	Intrathecal, neurostimulation
The Brain Trauma Foundation	http://tbiguidelines.org/glHome.aspx	Guidelines - Inhospital Severe TBI Guidelines - Surgical Management of TBI
Safer Roads	http://www.saferroads.org.uk/	No Guidelines
Rail Accident Investigation Branch	http://www.raib.gov.uk/about_us/index.cfm	No Guidelines
Oslo Sports Trauma Research Centre	http://www.klokeavskade.no/en/	No Guidelines
Oregon Evidence-Based Practice Centre	http://www.ohsu.edu/epc/pastProjects/index.htm N/A	Intrathecal pain, neurostimulation
Injury Prevention Network of Aotearoa New Zealand	http://www.ipnanz.org.nz/ N/A	Publications
Trauma Centre at Justice Resource Centre	http://www.traumacenter.org/ N/A	Publications
The DANA Foundation	http://www.dana.org/ N/A	Intrathecal pain Guideline, neurostimulation guideline

European Association for Injury Prevention and Safety Promotion	http://www.eurosafe.eu.com/ N/A	Guideline AND pain
New Zealand Injury Prevention strategy	http://www.nzips.govt.nz/resources/publications.php N/A	Resources/ Publications/
NHS Health at Work	http://www.nhsplus.nhs.uk/web/public/default.aspx?PageID=330	TAC Guidelines only
The Canadian Association of Road Safety Professionals	http://www.carsp.ca/index.php?0=page_content&1=59&2=134 N/A	Resources / Publications

Search 2: Identification of relevant studies for intrathecal implantable therapies using Google	
Find web pages that have **all these words**	pain AND (evidence OR guideline) AND (intrathecal OR intraspinal OR spinal OR subarachnoid OR subdural OR stimulation OR electrode OR implantable)
Limits	English, Past Year
Results 21/5/2008 completed search	About 2,410,000 results

Appraisal

Appraisal was undertaken in steps.

The most recent review (EBG, SR or HTA) was assessed for quality using standard appraisal criteria.

If found to be of high quality, it was cross checked against the other available reviews to compare scope (population and outcomes addressed) and consistency of findings

If found not to be of high quality, the next most recent was appraised and the above process repeated.

Quality

Evidence-based guidelines and systematic reviews were appraised using standard criteria by a single reviewer in consultation with colleagues as required. RCTs were also appraised using standard criteria by a single reviewer in consultation with colleagues as required. Details of quality appraisals are included in Appendix 5.

Systematic reviews

SRs were appraised using standard criteria applied by a single reviewer in consultation with colleagues as required. Data on characteristics of the studies were extracted and summarised.

Data Extraction

Data on characteristics of the studies were extracted and summarised.

Consistency of findings

Where a current, good quality review is available, the findings are compared with other sources of synthesised evidence that have been identified to determine whether any inconsistencies exist in the information provided.

APPENDIX 3: LIST OF INCLUDED STUDIES

1. Eisenach, J, Curry, R, Rauck, R, Pan, P, and Yaksh, T. Role of Spinal Cyclooxygenase in Human Postoperative and Chronic Pain. Anesthesiology. May 2010. 112 (5): 1225 -1233.

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APPENDIX 4: SUMMARY OF INCLUDED STUDIES

Table A4.1 summary of included studies

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
EVIDENCE-BASED GUIDELINES					
Institute for Clinical Systems Improvement 2007 Assessment and Management of Chronic Pain	**Population:** Physiologically mature adolescents (between 16-18 years) and adults. It can be applied to paediatric populations where noted. **Setting:** Not specified **Intervention:** Intrathecal medication delivery systems **Comparator:** Not specified **Outcomes:** None detailed **Inclusion:** None specified other than in the patient/population section **Exclusion:** It is not intended for the treatment of migraine headaches, cancer pain, advanced cancer pain, or in the context of palliative care or end-of-life management	EBG	Intraspinal therapy can provide an excellent therapeutic effect for nonmalignant and cancer pain. However, it should be reserved only for patients who have failed other conservative approaches for the treatment of pain, and should be used cautiously. Before starting intrathecal treatment in a patient with chronic pain, the expectations and plans should be discussed in detail. The best candidates are patients who respond well to oral opioids but who cannot tolerate the side effects (e.g., sedation, nausea, constipation). Only one observation study was included in this review which provides low level evidence. The results need to be interpreted with this in mind.	*Insufficient evidence to draw conclusions*	The concerns with this review include possible conflict of interest, the search strategy not being explicitly documented, and the validity of the trials not being assessed
Accident Compensation Corporation of New Zealand (ACC NZ) 2005 Interventional pain management	**Population:** People over the age of 12 years and were experiencing persistent non-cancer pain. **Setting:** Not specified **Intervention:** Continuous spinal infusion including the following sites: intrathecal, subarachnoid, and neuroaxial **Comparator:** Not specified **Outcomes:** Pain, adverse effects, function, medication use, work **Inclusion:** The following study types were considered for inclusion in the Interventional Pain Management (IPM) guidance: (1) systematic reviews, (2) guidelines, (3) health technology assessments, (4) randomised controlled trials/quasi-randomised controlled trials, concurrent control and case control studies with 10 or more subjects, (5) case series with 50 or more subjects, (6) cohort studies with 50 or more subject. However, case series and cohort studies with fewer than 50 subjects were included if they reported on adverse events or safety concerns associated with the intervention in question in the abstract. Evidence on harm is often weaker than that on benefits, so the sample size threshold for evidence about harm was therefore lowered.	EBG	"We do not recommend intrathecal infusion of opioids on their own for the treatment of adults with persistent pain of non-cancer origin." Only observation studies were included in this guideline which provides low level evidence. The results need to be interpreted with this in mind.	*Insufficient evidence to draw conclusions*	

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
	Only studies reported in the English language were included. In order to be included in the appraisal, studies were required to report on at least one pain-related primary outcome. **Exclusion:** All studies on healthy volunteers, or involving experimentally induced pain, were excluded. Studies were excluded if they reported on: pain due to malignancy; acute resolving pain such as post-operative pain; childbirth; dysmenorrhoea; dental pain; infection such as post-herpetic neuralgia; systemic inflammatory conditions; migraine; angina; other visceral pain; peripheral vascular disease; or haematological disorders. Studies that did not report pain control or pain relief as a primary outcome were excluded. Case studies involving < 50 subjects were excluded, unless they contained information on adverse effects or safety in the abstract. Studies graded as low quality or scoring low (if a case series) were excluded from the review of effectiveness.				
Sanders 2005 Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients.	**Population:** Chronic nonmalignant pain syndromes **Setting:** Not specified **Intervention:** Implantable infusion pumps **Comparator:** Not specified **Outcomes:** Pain, function, mood **Inclusion:** Studies that were prospective, control research design using quantifiable, objective outcome measures, including function. **Exclusion:** Not specified	EBG	Given the continual absence of quality research showing consistent and clinically significant evidence, the current guidelines do not recommend using implantable infusion pumps with Chronic Pain Syndrome patients. Only observation studies were included in this guideline which provides low level evidence. The results need to be interpreted with this in mind.	*Insufficient evidence to draw conclusions*	Although this research article is a guideline, we have appraised it using criteria for a systematic review. The limitations include not having a documented comprehensive search strategy and not appraising the included study using appropriate appraisal criteria.
SYSTEMATIC REVIEWS / HEALTH TECHNOLOGY ASSESSMENTS					
Noble 2010 Long-term opioid management for chronic non cancer pain	**Population:** Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least three months **Intervention:** • Intrathecal morphine alone or with clonidine, bupivacaine or midazolam • Intrathecal bupivacaine • Intrathecal sufentanil citrate	SR	"Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were	*Positive but needs further evidence on combination therapies and on long-term quality of life and functional status outcomes.*	*Note - This systematic review is not to be confused with a similar one published in 2008 by the same authors. However, the inclusion and exclusion criteria have been updated so this

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
	• Intrathecal methadone • Intrathecal midazolam • Intrathecal dilaudid • Intrathecal fentanyl • Intrathecal clonidine • Intrathecal baclofen **Comparator:** No comparator assessed as the studies included were case-series (observational). **Inclusion:** • Efficacy data on participants after at least 6 months of treatment; • In any language and were full text articles; • Were prospective; • Enrolled and administered to at least 10 participants; • Reported data of participants with CNCP lasting for at least 3 months; • Previous non opioid pharmacotherapy must have failed before beginning opioids; • No reporting of redundant data on patients who were also reported on in included studies or studies with duplicate data; • RCTs and pre-post case-series were included **Exclusion:** Not reported **Outcomes:** Average change in pain scores, patients with at least 50% pain relief, quality of life (QoL), function levels, AEs, discontinuation from study due to insufficient pain relief and discontinuation from study due to AEs.		rare."		evidence is new.
Teasell 2010 A Systematic Review of Pharmacological Treatments of Pain After Spinal Cord Injury	**Population:** Patients with mixed pain (neuropathic and musculoskeletal/spastic) **Intervention:** IT morphine and clonidine, IT baclofen **Comparator:** N/A **Inclusion:** • Studies were only included for analysis if at least 50% of subjects had an SCI, there were at least 3 subjects with an SCI, and there was a definable intervention being studied. Only studies published in the English language	SR	There is level 1 evidence from 1 RCT and level 2 evidence from a prospective controlled trial that a combination of intrathecal morphine and clonidine results in a significant reduction in neuropathic pain. There is level 4 evidence that intrathecal baclofen reduces musculoskeletal pain after SCI in conjunction with spasticity reduction.	*Insufficient evidence to draw conclusions*	

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
	were included. • Studies examining all types of pain after SCI (nocioceptive, neuropathic, mixed) were examined **Exclusion:** Not reported **Outcomes:** pain reduction (VAS, good to excellent scale)				
Patel 2009 Systematic Review of Intrathecal Infusion Systems for Long-Term Management of Chronic Non-Cancer Pain	**Population:** Patients with chronic non-cancer pain **Intervention:** Intrathecal morphine (+ buprenorphine, bupivacaine, clonidine, fentanyl, hydromorphone or methadone, NaCl) **Comparator:** No comparator assessed as the studies included were case-series (observational). **Inclusion:** • Studies should clearly show the use of intrathecal infusion device/system (programmable or fixed infusion rate) implanted for non-cancer pain for long-term use • Studies must have a specific indication for intrathecal infusion and the drug injected. • A minimum of 12 months of follow-up was available. • Clear documentation of patient outcomes and complications should have been provided. • Number of patients evaluated must be at least 25. **Exclusion:** • Lack of clear documentation of infusion systems or mixed delivery methods • Externalized infusion systems for short-term use. • Studies for non-cancer pain with less than 12 months follow-up. • Lack of clear documentation of the indications and patient population being studied. **Outcomes:** Pain reduction (%, VAS scale), satisfaction levels, QoL, work status, complications, number of doctor's visits, number of emergency visits, functional score QUALEFFO	SR	"Intrathecal infusion devices used for the treatment of chronic intractable pain provide positive long-term outcomes and may have a role as an advanced-stage therapy for refractory pain. The present systematic review with 5 observational studies meeting methodologic quality assessment (71-75) indicates that the evidence is Level II-3 or III (limited) based on USPSTF criteria with a recommendation of 1C/strong based on the evidence derived from observational studies". "Paucity of literature. There were no randomized trials available meeting the inclusion criteria. Further, observational studies are also very few."	*Positive but needs further evidence*	
Rauck 2009 Intrathecal	**Population:** Patients with chronic severe (non-cancer) pain	SR	"Evidence from case studies, case series, open-label studies, and DBPC trials suggests that ziconotide, as either	*Positive but needs further evidence*	

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
Ziconotide for Neuropathic Pain: A Review. Pain Practice	**Intervention:** IT ziconotide, IT Ziconotide with baclofen **Comparator:** No comparator assessed as the studies included were case-series (observational). **Inclusion:** • For clinical studies, both controlled (randomized or nonrandomized) and uncontrolled studies (case series or case reports) were included. • Patients with any type of neuropathic pain condition. Male and female patients of all ages and races/ethnicities were included. • IT administration of ziconotide for neuropathic pain, in any dose, alone or in conjunction with one or more drugs. • Pain assessment as an outcome measure **Exclusion:** Not reported **Outcomes:** VASPI score, AEs, cerebrospinal fluid (CSF) concentrations , medication use, functional status		monotherapy or in combination with other IT agents, can be effective in treating patients who have refractory neuropathic pain….Additional studies evaluating the long-term efficacy and safety of ziconotide for neuropathic pain may be warranted".	*in long-term studies*	
Wallace 2009 Ziconotide Combination Intrathecal Therapy: Rationale and Evidence	**Population:** Patients with chronic pain **Intervention:** • IT morphine alone or with IT ziconotide, IT hydromorphone with IT ziconotide, • IT baclofen with IT ziconotide, • IT hydromorphone or fentanyl or sufentanil or bupivacaine or clonidine or baclofen with IT ziconotide **Comparator:** N/A **Inclusion:** Not reported **Excluded:** Not reported **Outcomes:** VASPI score, AEs	SR	"Clinicians must balance the lack of evidence-based data with their own clinical expertise and experience with ziconotide and other IT agents when designing IT therapy regimens. There is a need for additional evidence-based investigations of ziconotide combination therapies, including long-term clinical trials".	*Insufficient evidence to draw conclusions*	
Noble 2008 Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and	**Population:** Patients with chronic noncancer pain refractory to treatment for at least 3 months **Setting:** Not specified **Intervention:** Long-term opioid therapy (oral, transdermal and/or intrathecal) **Comparator:** Not specified **Outcomes:** Pain ,withdrawal rates, adverse effects	SR	"Many patients in the included studies were so dissatisfied with adverse events or insufficient pain relief from opioids that they withdrew from the studies. For patients able to continue on opioids, evidence (albeit weak) suggests that their pain scores were lower than before therapy began and that this relief could be maintained long-term (≥6 months). However, data describing long-term safety and efficacy of	*Insufficient evidence to draw conclusions*	Only long-term opioid therapy studies were included which would mean studies with shorter term outcomes would be missed. Only 6 studies were included in this

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
safety	**Inclusion:** Studies that (1) collected data on patients after at least 6 months of opioid therapy; (2) were published in English; (3) were reported as full-text articles; (4) did not include patients also reported on in other included studies; (5) were prospective; (6) enrolled at least 10 patients; (7) enrolled only patients who had chronic noncancer pain (CNCP), defined as pain lasting at least three months as defined by International Association for the Study of Pain (IASP). There were also two additional criteria for pain outcomes: (1) pain outcomes must have been patient-reported; and (2) outcome data must not have been collected retrospectively. **Exclusion:** Not specified		opioids for CNCP are limited in terms of quantity and quality, precluding the formation of evidence-based conclusions supported by strong qualitative or stable quantitative evidence. An evidence base of low quality provides only weak evidence from which to draw qualitative conclusions and only low-stability evidence from which to draw quantitative conclusions. The generalisability of findings of these studies to ''real-world'' patients with chronic non-cancer pain in general is unclear. Prescreening of patients in intrathecal studies for opioid responsiveness prior to commencement of treatment may limit the generalisability of the findings of these studies to patients who are not prescreened. We conclude that many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief; however, weak evidence suggests that intrathecal opioids reduce pain long-term in the relatively small proportion of individuals with CNCP who continue treatment." Only observation studies were included in this review which provides low level evidence. The results need to be interpreted with this in mind.		review, but correspondence with review authors provided valid explanations for reasons for exclusion of other potentially relevant studies.
Turner 2007 Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications.	**Population:** Patients with chronic non-cancer pain **Setting:** Not specified **Intervention:** Programmable intrathecal opioid or ziconotide delivery systems **Comparator:** Not specified **Outcomes:** Pain, adverse effects, function, medication use, work **Inclusion:** Studies that: (1) were published in English (published conference abstracts were excluded); (2) addressed pain treatment with opioid or ziconotide delivered intrathecally via programmable pumps; (3) patient diagnoses not limited to spasticity or specific diseases (e.g. cancer, sickle cell disease); (4) contained original data on pain, functioning, or complications in humans. Also: (1) the only pump studied was programmable or data were presented separately for patients with programmable pumps; and (2) the first medication delivered was intrathecally was an opioid (with or without adjuvant	SR	The studies reviewed found improvement in pain and functioning on average among patients with chronic noncancer pain who received permanent implantable intrathecal infusion pumps. However, their methodologic limitations preclude conclusions concerning the effectiveness of this technology long-term and as compared with other treatments. Drug side effects and hardware complications were common. Suggestions are made for methodologic improvements in future studies. Only observation studies were included in this review which provides low level evidence. The results need to be interpreted with this in mind.	*Insufficient evidence to draw conclusions*	No studies of ziconotide met the inclusion criteria for either effectiveness or the complications review

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
	medications) or ziconotide. For the effectiveness review (but not the complications review) studies also had to be either RCT, controlled trial or cohort study, or other studies which had (1) independent observer-completed or patient-completed standardised measures of pain or functioning obtained both before implantable drug delivery system (IDDS) implantation and at planned, regular follow-ups; (2) data from patient baseline descriptive and outcomes measures reported fro all study participants who underwent pump implantation during the study period; and (3) original data reported on pain or functioning before IDDS implantation and for ≥75% of implanted patients at a follow-up ≥ 6 months. **Exclusion:** (1) more than 10% of the sample were being treated for spasticity or pain associated with a specific disease and data on pain, functioning or complications were not presented separately for patients without these conditions; (2) study focused only on patients who did not respond to the first IDDS drug they were given; (3) case reports.				
Hayes Inc. 2006 Intrathecal opioid therapy for chronic nonmalignant pain	**Population:** Patients with chronic non-malignant pain **Setting:** Not specified **Intervention:** Intrathecal opioid therapy delivered via implantable infusion pump **Comparator:** Not specified **Outcomes:** Pain, adverse effects, function, medication use, work, costs **Inclusion:** Studies with sample size >20 **Exclusion:** Studies with sample size <20	HTA	The limited available evidence suggests that intrathecal morphine or hydromorphone delivered via implanted infusion pump can provide substantial pain relief and improve quality of life for some patients with chronic, intractable, nonmalignant pain syndromes. Several of the studies found a greater effect for patients with nociceptive pain compared with patients with neuropathic or deafferentation pain, but other studies failed to find a differential effect according to type of pain. Drug tolerance was reported in a number of studies and a number of drug-related side effects were described, although device-related complications appeared to be a more serious problem in most studies, with many of these complications necessitating surgery. Additional studies are needed to address questions regarding the safety, optimal drug dosage, and long-term benefit of intrathecal opioid therapy. Therefore a Hayes Rating of C has been assigned for intrathecal opioid therapy delivered via implantable pump in patients with chronic non-malignant pain who have failed other less invasive forms of pain management. A Hayes Rating of C means Potential but unproven benefit. Use of the technology is supported by some positive published data regarding safety and/or efficacy	*Insufficient evidence to draw conclusions*	One of the faults of the review was that the search strategy was not comprehensive. The search terms used were limited and we cannot therefore exclude the possibility of relevant articles being missed. This does appear to be case as studies which have been included in other reviews, were not included in this review. In addition, there criteria used to appraise the quality of the individual studies was not explicit. Low level studies included as these appear to be the only studies undertaken in this area.

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
			for the cited application(s) Only observation studies were included in this review which provides low level evidence. The results need to be interpreted with this in mind.		
WorkSafe BC 2005 Intrathecal fentanyl for chronic nonmalignant pain	**Population:** Chronic non-malignant pain patients **Setting:** Not specified **Intervention:** Intrathecal fentanyl **Comparator:** Not specified **Outcomes:** Pain, adverse effects, function, medication use, costs **Inclusion:** Studies that: • human adult subjects. • at least the abstract was available in English. **Exclusion:** • publications on intraspinal fentanyl or morphine without additional clarification, whether it was epidural or intrathecal were excluded. • systematic review/review articles were excluded if the methodology used to evaluate the quality of the primary studies were not apparent	SR	All of these studies involved patients with failed back surgery. These studies suggest that there may be some low level evidence on the effectiveness of intrathecal morphine in the long-term treatment of chronic nonmalignant pain. However, the evidence is still inconclusive due to the variability in outcome criteria/measurement tools, follow-up periods and the supplemental use of other analgesics, antidepressants or sedatives. .	*Insufficient evidence to draw conclusions*	No studies found which used IT fentanyl. It is of interest that some of these studies demonstrate dose escalation of up to 20 times, from the start of the trial to the end of the follow-up period
Jadad 2001 Management of Chronic Central Neuropathic Pain Following Traumatic Spinal Cord Injury	**Population:** Central neuropathic pain (CNP) following Traumatic Spinal Cord Injury (TSCI) **Setting:** Not specified **Intervention:** Any pharmacological intervention **Comparator:** Not specified **Outcomes:** Pain, adverse effects **Inclusion:** Studies that were: (1) in humans, (2) about the cause, management, or measurement of CNP in individuals after TSCI. **Exclusion:** (1) children younger than 13 years; (2) studies where the sample consisted of people without a Traumatic Spinal Cord Injury (TSCI) or chronic neuropathic pain; (3) inability to determine whether chronic pain was central and neuropathic; (4) studies where the sample included individuals with TSCI as well as other types of CNP, but where the results were not presented	HTA/SR	Only one observation study was included in this review which provides low level evidence. The results need to be interpreted with this in mind. In sum, research on pharmacological interventions for the management of CNP after TSCI is in its infancy. The evidence available is so limited that it is impossible to draw any conclusions regarding their role in clinical practice. Although it appears that local anaesthetics, opioids, and clonidine given spinally may play a role in the management of CNP after TSCI, the evidence available comes from few, small, poorly reported, and largely uncontrolled studies.	*Insufficient evidence to draw conclusions*	

1st author, year, title	Inclusion, Exclusion criteria (for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category	Other comments
	separately for individuals with TSCI; (5) studies that only used the term "chronic pain" without any other description of the pain experienced by the individuals in the study sample that could have helped us judge it as central and neuropathic.		Findings suggest that intrathecal baclofen does not decrease chronic neurogenic spinal cord pain		
Williams 2000 Intrathecal pumps for giving opioids in chronic pain: a systematic review	**Population:** Patients with chronic cancer and non-cancer pain **Setting:** Hospital, hospice or community setting **Intervention:** • Different types of intrathecal pump systems for giving opioids in chronic pain control • Different types of intrathecally administered drugs given by pump systems (e.g. opioids, local anaesthetics, clonidine, midazolam, noradrenaline) **Comparator:** Other routes of analgesia delivery (e.g. oral, subcutaneous, rectal, intramuscular, intravenous, transdermal, intraventricular, neuroablative, neurolytic and neurosurgical interventions) **Outcomes:** Pain, adverse effects, function, medication use, work, costs **Inclusion:** Chronic cancer and non-cancer pain **Exclusion:** All acute pain was excluded, e.g. labour, postoperative and trauma pain	HTA/SR	There was no conclusion made just for non-cancer patients. Only observation studies were included in this review which provides low level evidence. The results need to be interpreted with this in mind.	*Insufficient evidence to draw conclusions*	The areas of concern are non-reproducible search strategy (no search terms have been documented) and not reporting appraisals of the study and the impact this may have on the results. In addition, some studies appear to have not been included in the non-cancer group.
RANDOMISED CONTROLLED TRIALS					
Eisenach 2010 Role of Spinal Cyclooxygenase in Human Postoperative and Chronic Pain	**Population:** Patients with chronic pain, already receiving IT morphine for at least 6 weeks **Intervention:** IT morphine with IT ketorolac **Comparator:** Normal saline placebo **Outcomes:** • Pain intensity and unpleasantness (VAS and thermal testing), proportion of patients who experienced ≥30% or 50% pain relief, AEs	RCT	"We failed to observe greater analgesia from intrathecal ketorolac than saline placebo in patients with primarily low back and lower extremity pain and a combination of somatic and neuropathic components" "2mg of intrathecal ketorolac was not associated with serious side effects, failed to reduce ongoing pain in chronic pain patients more than placebo….These observations are limited by the small number of subjects studied, and patient population, and the amount and timing of ketorolac dosing. They… suggest that spinal cyclooxygenase is not activated in most patients with these clinical pain conditions."	*Neutral (no difference in effect between interventions)*	

APPENDIX 5: APPRAISAL TABLES

Table A5.1 Critical appraisal table *(Noble, M, 2010)*

Study: Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic non cancer pain. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006605. DOI: 10.1002/14651858.CD006605.pub2.	
Description of study: *Systematic review of RCTs (or other types of studies).*	
Patient/population	Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least three months.
N	n = 231 (10 studies) **Please note all these studies may not have assessed our outcomes of interest.**
Setting	Participants were treated on an outpatient basis, with the exception of screening and implantation phases of intrathecal studies.
Intervention/indicator	

Reference	**Intervention**
Anderson 1999; (case series) n=30	Intrathecal morphine
Anderson 2003; (case series) n=27	Intrathecal morphine
Angel 1998; (case series) n=11	Intrathecal morphine
Hassenbusch 1995; (case series) n=18	Intrathecal morphine or intrathecal sufentanil citrate
Kumar 2001; (case series) n=16	Intrathecal morphine, with clonidine if needed
Mironer 2001; (case series) n=24	Intrathecal methadone
Pimenta 1998 (case series) n=11	Intrathecal morphine clorhidrate (n = 10) or tramadol (n = 1)
Rainov 2001; (case series) n=26	Intrathecal morphine with bupivacaine (n = 20) and/or clonidine (n = 16) and/or midazolam (n = 10)

	Shaladi 2007; (case series) n=24	Intrathecal morphine
	Thimineur 2004; (case series) n=38	Intrathecal morphine (n = 9), Intrathecal Dilaudid (n = 21), Intrathecal fentanyl (n = 24), Intrathecal clonidine (n = 23), Intrathecal baclofen (n = 2), Intrathecal bupivacaine (n = 1), Intrathecal methadone (n = 1)
Comparison/control	None	
Outcomes	"We assessed adverse events (side effects), discontinuation from study due to adverse events, discontinuation from study due to insufficient pain relief, average change in pain score, proportion of patients with at least 50% pain relief, health-related quality of life, and function". Outcome measures must have been validated or used as a standard of care to be included in the analyses. In addition to these general inclusion criteria, we employed two criteria for pain outcomes: 1. Pain and quality-of-life outcomes must have been patient reported; 2. Outcome data must not have been collected retrospectively (for example, post-treatment surveys/questionnaires), because reports based on memory of pain may differ from reports given at the time that pain is experienced (Eich 1985; Linton 1983). For participants who discontinued participation before the end of the study, we intended to collect data on duration, dose, titration, and rotation of opioids from before they withdrew from the study. However, these data were generally not available in the publications we identified."	
Inclusion Criteria	**Types of studies** 1. Randomized controlled trials (RCTs) and nonrandomized controlled trials. 2. Pre-post case-series studies (including long-term open-label continuations of short-term RCTs) 3. Studies that enrolled and administered opioids to at least 10 participants. 4. Prospective studies or studies that could not definitively be determined to be prospective after unsuccessfully attempting to query their authors because we believe their exclusion could not be justified. 5. Full-text articles only 6. Any language **Types of participants** • Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least three months (that is, meeting the IASP definition for chronic	

	pain) prior to trial enrolment. Previous non-opioid pharmacotherapy must have failed before beginning opioids. • Types of interventions • Any opioid taken by any route in any dose for at least six months. • Types of outcome measures • Adverse events (side effects), discontinuation from study due to adverse events, discontinuation from study due to insufficient pain relief, pain score, health-related quality of life, and function. Outcome measures must have been validated or used as a standard of care to be included in the analyses. • Pain and quality-of-life outcomes must have been patient-reported "We searched for studies that: collected efficacy data on participants after at least 6 months of treatment; were full-text articles; did not include redundant data; were prospective; enrolled at least 10 participants; reported data of participants who had CNCP. Randomized controlled trials (RCTs) and pre-post case-series studies were included". "Prospective, full text, and any language In more detail, the authors elaborated on the type of studies which were included "we only found one controlled trial that evaluated the efficacy and safety of opioids for CNCP and reported long-term outcomes. That study compared two opioids and was not controlled using placebo or a non opioid treatment." "We defined long-term open label continuations of short-term RCTs as case-series studies" "Previous non opioid pharmacotherapy must have failed before beginning opioids".	
Exclusion Criteria	No meeting abstracts or poster presentations were included. "We did not include redundant data on participants who were also reported on in other included studies, nor did we include studies with duplicate data". Studies where outcome data has been collected retrospectively.	
Study Validity.		
Is it clear that there were no conflicts of interest in the writing or funding of this review?	Yes	Declarations of interest were stated as "none known" and Sources of support were stated as "internal sources – ECRI Institute, USA and external sources – The Mayday Fund, USA". It was not reported whether the reviewers were blind to authors of articles that they were reviewing, however none of the authors of the SR were authors of studies on the included and excluded studies list.

Does the review have a clearly- focused question?	Yes	"The purpose of this systematic review is to summarize the evidence pertaining to the efficacy and safety of long-term opioid therapy for CNCP. Specifically, we seek to: 1. Determine the effectiveness of long-term opioid therapy for CNCP; 2. Identify the adverse effects of long-term opioid therapy for CNCP; and 3. Assess withdrawal rates from treatment by reasons for withdrawal based on patient statements."
Is a systematic review the appropriate method to answer the question?	Yes	
Does the review have specified inclusion/exclusion criteria?	Yes	As above
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Does the review document a comprehensive search strategy?	Yes	
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Were 2 or more independent reviewers used for: **1. application of inclusion criteria to assess eligibility of studies?**	Yes	"Two review authors screened abstracts of all identified studies against the inclusion criteria (MN, PW).We retrieved all possibly relevant articles in full text for comprehensive assessment of internal validity (quality) and satisfaction of inclusion criteria."
2. extraction of data from study	Yes	"Two review authors (MN, CA) independently extracted data from English-language articles.

reports?		Discrepancies were settled by consensus. Data from non-English language articles were extracted by volunteers affiliated with The Cochrane Collaboration."
3. appraisal of study quality?	Yes	"Two review authors (MN, CA) independently extracted data from English-language articles. Discrepancies were settled by consensus. Data from non-English language articles were extracted by volunteers affiliated with The Cochrane Collaboration."
Were the strengths and limitations of included studies and potential impact on the results discussed?	Yes	"Some of the quantitative estimates were not robust, meaning that an estimate of the treatment effect size cannot be accurately estimated with the currently available evidence, and the estimates may therefore be unstable and should be interpreted cautiously. The low internal validity ratings indicate that the evidence supporting our conclusions is highly subject to change and that the likelihood is high that findings of future studies may overturn these conclusions. Furthermore, there may be a particular risk of publication bias in uncontrolled case-series studies, as journals may be less likely to accept studies of this design, investigators may be less likely to submit them for publication (given the lesser financial investment in conducting them), and no clinical trial registry for uncontrolled studies is currently in widespread use." "Investigation (of heterogeneity) was possible for intrathecally-administered opioids, and potential relationships between proportion of participants with clinically significant pain relief (> 50%) and year of publication and prospective study design, and between average pain relief and predominant cause of pain in the study, were identified. However, these relationships do not seem stable. The only convincing covariate we identified was a lower rate of discontinuation due to adverse events from clinical study in studies that administered oral weak opioids compared with studies that administered strong oral opioids." "Predominant cause of pain was the only factor significantly associated with the SMD (P = 0.01). As a robustness test, we repeated the regression using three other meta-regression models (i.e., fixed-effect, method of moments, unrestricted maximum likelihood), which consistently showed significant findings. Failed back surgery syndrome (k = 5) was associated with the least amount of pain relief, unspecified (k = 2) and neuropathic pain (k = 1) were associated with more pain relief,

		and osteoporotic vertebral fractures (k = 1) were associated with the most pain relief. However, the fact that few studies were available for three of the four causes of pain undermines the stability of this finding."
Was the validity of included trials appraised using appropriate criteria?	Yes	"Two review authors (MN, CA) independently assessed the internal validity of English-language studies (non-English language articles were assessed by volunteers affiliated with The Cochrane Collaboration). Discrepancies were resolved by consensus. We assessed the risk of bias in included studies using a 10-question internal validity assessment instrument developed by methodologists at ECRI Institute for the assessment of case series using domains identified as important factors by experts in the field (Table 1; AHRQ 2002; Deeks 2003; Egger 2003). To evaluate long-term, open-label case series that were continuation studies of short-term RCTs, we consulted the original publication of the RCT whenever necessary (see 'Characteristics of included studies' for original citations)."
Is there a summary of the results of individual studies?	Yes	
If meta-analyses were conducted, was it reasonable to do so?	Yes	
If meta-analyses were conducted, was it done appropriately?	Yes	"We performed sensitivity analyses on evidence bases comprised of at least three studies. Evidence bases consisting of only one or two studies were considered to inherently lack robustness."
Other		
What is the overall risk of bias?	Low	"For analyses without substantial heterogeneity ($I^2 < 50\%$) and at least 10 studies, we planned to use the "trim and fill" method to test for funnel plot asymmetry, which suggests missing studies, possibly due to publication bias (Duval 2000a; Duval 2000b). However, none of the evidence bases for any of the outcomes met these criteria, precluding an investigation on publication bias." Selection bias cannot be ruled out of the analysis as data from uncontrolled case series was used and this could have led to the possible unexplained heterogeneity in the outcomes assessed, as

		well as the overall treatment effect size. "We considered data from uncontrolled case series should be kept in mind when considering the studies' results; influences from regression to the mean and selection bias cannot be ruled out. Furthermore, case series data cannot be extrapolated to draw conclusions regarding comparative effectiveness." Hence, the different drug types cannot be assessed as being more superior to one or the other.

Results.

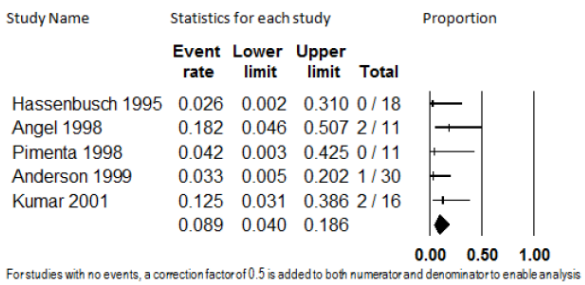
Side effects of IT opioids

Ten studies which included a total of 228 patients, the most common adverse events (AEs) included pump and catheter malfunctions and malpositioning, surgical complications, and postsurgical complications. The highest amount of device complications requiring reoperation was reported as 27 % (Hassesnbusch). Two studies reported a total of six deaths, with one death described as a neuropsychological event, suicide (Thimineur et al, 2004).

Discontinuation from study due to AEs

Five studies which included a total of 86 patients assessed discontinuation from the trial due to AEs. The pooled effect rate was 8.9% [95% CI: 4.0% to 26.1%], and was not substantially heterogenous (Figure 3).

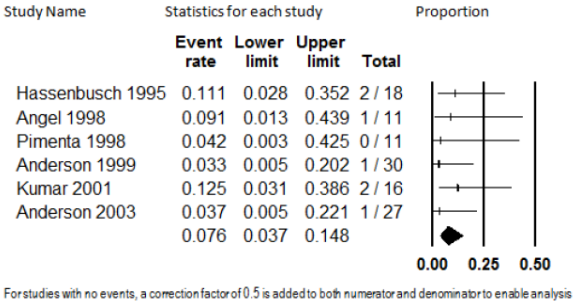
Figure 3. Discontinuation from Intrathecal Opioids Studies due to Adverse Events, Follow-up 20 months (mean) to 29 months (mean) (I^2<0.001)



Discontinuation from study due to insufficient pain relief

A total of 6 studies which included 113 patients documented discontinuation due to insufficient pain relief. The overall event rate was 7.6% (95% CI: 3.7% to 14.8%). No substantial heterogeneity was detected (I2 < 0.001), and the estimate was robust to sensitivity analyses (see figure 6).

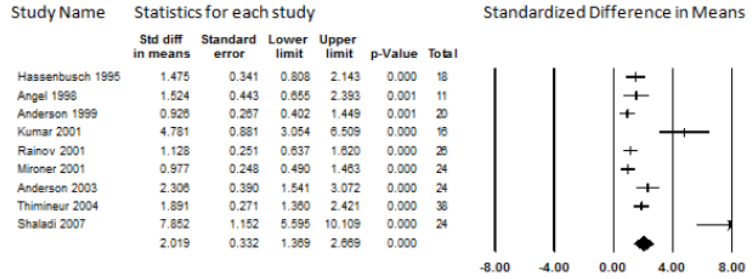
Figure 6. Discontinuation from Intrathecal Opioids Studies due to Insufficient Pain Relief, Follow-up 6 to 29 months (mean) (I^2<0.001)



Average change in pain scores throughout treatment

A total of 9 studies involving 220 patients assessed the mean change in pain scores from baseline after administration of intrathecal opioids. At baseline, the pooled score of the studies was 8.70 (95% CI: 8.37 to 9.04), which was an indication of severe pain. After follow-up, at the longest duration of treatment, this pooled score of the studies decreased to 4.45 (95% CI: 3.44 to 5.47), an indication of moderate pain. The overall effect size of the nine studies was 2.01 (95% CI: 1.37 to 2.66) (see below). Individually, the studies showed clinically significant mean reductions in pain score, however a considerable amount of heterogeneity was present, I2 = 87.1%. After univariate meta-regression analysis, the predominant cause of pain was significantly (P= 0.01) related to the change in pain score.

Figure 11. Change in Pain Score from Baseline, Intrathecal Opioids, Follow-up 6 months to 29 months (mean) (I^2=87.1%)

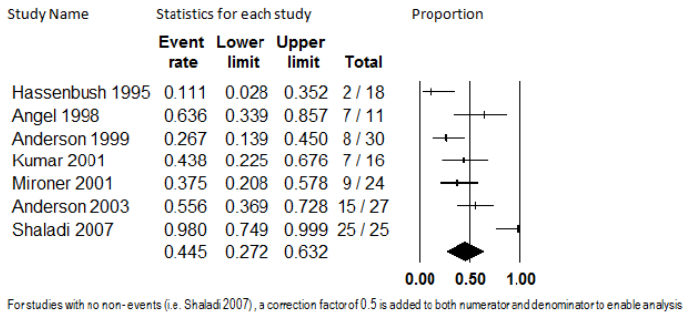


Pts with at least 50% pain relief

Seven studies including a total of 151 patients provided an indication of the proportion that experience at least 50% pain relief. The overall event rate for the seven studies was 44.5% (95% CI: 27.2% to 63.2%), with a reflected heterogeneity of 71.7%. Multiple meta-regression analyses found that the year of study publication was associated with a larger proportion of participants with at least 50% pain relief (P = 0.02).

When the model was corrected for publication year, heterogeneity was reduced but was still considerable at 52.2%.

Figure 12. Proportion of Patients with at least 50% Pain Relief, Intrathecal Opioids, Follow-up 6 months to 29 months (mean) (I^2=71.7%)

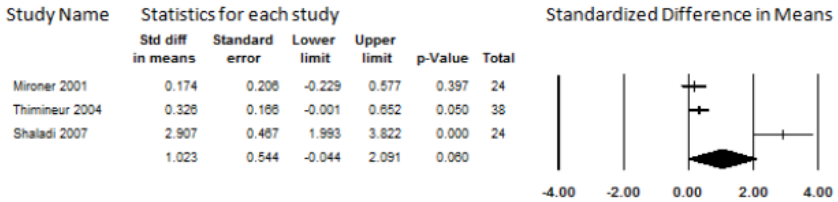


For studies with no non-events (i.e. Shaladi 2007), a correction factor of 0.5 is added to both numerator and denominator to enable analysis

Quality of life (QoL)

Three studies with a total of 92 patients assessed quality of life following long-term administration of intrathecal opioids, all using different instruments for measurement - the Tollison Quality of Life Scale (Mironer 2001), the SF-36 (Thimineur 2004), and the Questionnaire of the European Foundation for Osteoporosis (Shaladi 2007). Hence, it was not startling that each study revealed different outcomes. One of the studies had inconclusive findings (Mironer 2001), one reported a small benefit (Thimineur 2004), and one reported a large benefit (Shaladi 2007). The overall effect size in the combined meta-analysis was SMD 1.02, with a large 95% CI -0.04 to 2.09. Heterogeneity among them was substantial (I2 =93.4%) but due to the small number of studies could not be investigated.

Figure 16. Change in Quality of Life from Baseline, Intrathecal Opioids, Follow-up 6 to 36 months (I^2=93.4%)



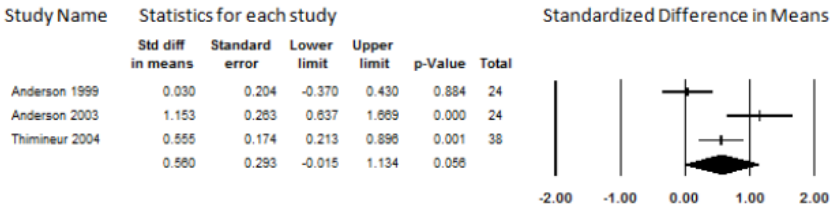
Assumed correlation coefficient of 0.5.

Functional status levels

Again, only 3 studies assessed functional status, involving a total of 98 patients initially and at follow-up this was reduced to 82 patients. Three different instruments were utilised to assess functional status, the Oswestry Disability Index (Thimineur 2004), the short form Sickness Impact Profile (Anderson 2003), and the Chronic Illness Problem Inventory (Anderson 1999). Study findings were inconsistent with one study being inconclusive (Anderson 1999), another revealing a moderate effect size (Thimineur 2004), and another revealing a larger effect size (Anderson 2003). The overall SMD was 0.56 (95% CI -0.02 to 1.13),

statistically inconclusive and heterogeneity was considerably high at 81.2%, however due to the small number of studies could not be investigated.

Figure 17. Change in Function Levels from Baseline, Intrathecal Opioids, Follow-up 6 to 36 months (I^2=81.2%)



Assumed correlation coefficient of 0.5.

Author's Conclusions.

"Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare."

Implications for practice

"Concern that an individual with CNCP may develop dependence on the drug during long term administration represents a potential barrier to treatment. However, the rate of observed signs of opioid addiction was extremely low in the body of evidence considered in this review (0.27%, conservatively). This rate would be 0.14% if no addictive behaviours occurred among the studies that did not mention addiction rates at all. Only three participants were reported as having potential abuse problems."

"In the interest of capturing the overall effect of opioid therapy on quality of life, we sought to analyse health-related quality-of-life outcomes in this review. However, findings on quality of life were inconclusive for all modes of administration.

Implications for research

"Protocols should specify uniform diagnostic and data collection criteria (e.g., pain etiology, drugs prescribed, dosing regimens) and mimic clinical practice (e.g., drug combinations could be used, drug changes could be made, drug dosage could be titrated slowly and adjusted, adverse effects could be aggressively managed).

Reasons for discontinuation, including satisfied departures, must be documented."

"Studies should always report data needed for meta-analysis (mean, standard deviation, number of participants, or data to calculate them), and authors of studies for which these data were not originally published should consider making them publicly available. Studies should also use validated scales, report intention-to-treat data in addition to completer analyses, and conduct post-hoc analyses to identify prognostic factors for treatment success."

Our Comments/Summary.

This systematic review was of high quality considering that the evidence base of included studies was weak. In light of this, the authors investigated the heterogeneity using sensitivity analyses finding that a relationship was present with the proportion of participants with clinically significant pain relief (> 50%) and year of publication and prospective study design, and between average pain relief and predominant cause of pain in the study. In terms of generalisability it is difficult to say with any level of certainty if the overall treatment effect for the various outcomes is representative due to attrition rates. The authors did not discover any studies which assessed prognostic factors for patient drop out.

The potential bias in the review was low. Missing data and studies could not be detected due to the small studies available. Hence, quantitative estimates provided from the analyses in the review do not provide a true reflection of the treatment effect size and as the authors say should be interpreted with caution.

Diversity in systematic review design, i.e. a review in The Cochrane Library vs. other peer-reviewed journals, allowed the authors to include outcomes including health-related quality of life and functional status in this review. This is in contrast to other systematic reviews involving similar inclusion/exclusion criteria but only focusing on outcomes of pain relief and patient satisfaction and adverse events. Higher quality assessment in this review using prospective studies, lead the authors to reclassify previous studies included as retrospective after personal communication with study authors. Methodologically, meta-regression was altered in this review to use five studies rather than ten studies in a previous systematic review. With the small number of prospective studies, this allowed relationships to be explored between patient characteristics/covariates and outcomes being assessed.

This SR was broader in its scope than the question we were required to answer, not solely investigating long-term intrathecal opioids but also oral and transdermal opioids in the management of non-cancer pain. The included studies for intrathecal opioids used case series as a study design, thus no controlled studies were assessed.

Overall, the risk of bias was low, resulting in a high quality SR which will be used for our report. Although the evidence base of included studies was weak, the appraisal of the included studies was of a high standard.

Table A5.2 Critical appraisal table *(Eisenach, J, 2010)*

Study: Eisenach, J, Curry, R, Rauck, R, Pan, P, and Yaksh, T. Role of Spinal Cyclooxygenase in Human Postoperative and Chronic Pain. Anesthesiology. May 2010. 112 (5): 1225 -1233.		
Description of study: Randomised control trial		
Patient/population	Patients with chronic pain, already receiving IT morphine for at least 6 weeks	
N	Total of 12 with each patient randomised to receive either saline or 2mg ketorolac on the first visit, with the alternative treatment on their second visit.	
Setting	Outpatient centre	
Intervention/indicator	IT morphine (mean 9.8mg; range 1.3 – 50mg/day) with IT ketorolac (2.0mg)	
Comparison/control	Saline + IT morphine (mean 9.8mg; range 1.3 – 50mg/day)	
Outcomes	Pain intensity (pain score and ≥30% or 50% pain relief), unpleasantness and adverse events	
Inclusion Criteria	Not clear, however all patients had American Society of Anesthesiologists physical status 1, 2, or 3; no history of allergy to ketorolac, morphine or bupivacaine; patients receiving IT chronic morphine for at least 6 weeks duration.	
Exclusion Criteria	Not reported	
Study Validity		
Is it clear that there are no conflicts of interest in the writing or funding of this study?	Yes	Supported, in part, by grant GM48805 from the National Institutes of Health, Bethesda, Maryland.
Does the study have a clearly focused question?	Yes	To test the role of spinal cyclooxygenase in human postoperative and chronic pain with IT injection of NSAID ketorolac.
Is a RCT the appropriate method to answer this question?	Yes	Initial studies in animals showed that commercially available ketorolac is safe and following these studies, human studies with IT ketorolac showed no significant adverse events but also showed no reduction in pain due to acute noxious heat stimuli or topical capsaicin. However, the effectiveness of IT ketorolac in states of central sensitization such as chronic pain was not known, hence an RCT testing this was the appropriate method.

Does the study have specified inclusion/exclusion criteria?	Yes	See above.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Did the study have an adequate method of randomisation?	Yes	"Patients were randomized, using a computer-generated series of random numbers, to receive either preservative-free ketorolac (2 mg) or saline on their first visit, with the alternative treatment on their second visit."
Was allocation to intervention group concealed?	Not reported	
Were patients blind to intervention group?	Yes	
Were investigators and care providers blind to intervention group?	Yes	"Patients were randomized, using a computer-generated series of random numbers, to receive either preservative-free ketorolac (2 mg) or saline on their first visit, with the alternative treatment on their second visit. The intrathecal injection solution was prepared by an individual not involved in the patient's care or research evaluation."
Were outcome assessors blind to intervention group?	Yes	The authors were contacted by email and stated that the outcome assessors were blind to the intervention group.
All outcomes were measured in a standard, valid and reliable way?	Partial	"Patients reported pain using a standard 10-cm visual analog scale (VAS) before injection and at the times of blood pressure monitoring... In addition, VAS pain assessments to heat stimuli applied to the skin on a lower extremity at a site without spontaneous pain were obtained using a commercially available Peltier-controlled thermode". No reference to any studies using the VAS scale or thermode was made. Additionally, the authors of the study did not report if they had used these measures previously resulting in valid outcomes.

Were outcomes assessed objectively?	Partial	The VAS scale can be interpreted in a subjective fashion as the patient reports their own view of pain in terms of highest to lowest pain. The thermal nociceptive testing is also a product of the patient's own view of pain reflected as a score on the VAS scale, hence there is subjective interpretation. Although, these outcome measures are not objective, they are however appropriate in terms of the field of study being pain.
Were outcomes assessed independently?	Yes	The authors were contacted by email and stated that the outcomes were assessed independently
Were the groups similar at baseline with regards to key prognostic variables?	Yes	"The 12 subjects recruited into the randomized, controlled, chronic pain study (five women and seven men) were 51 ± 9-yr old, 174 ± 10 cm tall, and weighed 91 ± 9 kg. Duration of pain was 12 ± 2 yr (range, 5–23 yr; mean ± SD)." "All subjects had back or leg pain, three were associated with degenerative disc disease, one was associated with chronic regional pain syndrome of the lower extremities, and one was associated with phantom leg pain. In all patients, the catheter tip was in the low thoracic intrathecal space."
Aside from the experimental intervention, were the groups treated the same?	Yes	The authors were contacted and asked, stating that the groups were treated in a similar fashion.
Were the outcomes measured appropriate?	Yes	Pain intensity was the primary outcome (measured with VAS pain scale). Other outcomes included blood pressure and heart rate due to the drug being experimental in human with chronic pain.
Was there sufficient duration of follow-up?	Partial	Authors report that "Subjects were discharged and contacted daily for 2 days, then 1 week after the study and questioned about neurologic symptoms, symptoms of postdural puncture headache, or other complaints."
Was there ≤20% drop-out?	Yes	All patients remained in the study from the beginning to the conclusion, possibly due to financial incentive - "Patients were paid $50 for completion of the first study day and an additional $100 for completion of the second study day". One patient committed suicide 6 months after the study completion.
Was the study sufficiently powered to detect any	Yes	"Based on our previous studies in patients with chronic pain,9–11 a study of 12 individuals was planned to distinguish an average difference in pain scores over the time of testing between placebo and

differences between the groups?		ketorolac of 2.2 with an α of 0.05 and 1 - β of 0.8, assuming a mean pain score of 5 in the control condition and a group SD of 2.5."
If statistical analysis was undertaken, was this appropriate?	Yes	"Data are presented as mean ± SEM unless otherwise indicated. The effects of intrathecal injections over time were determined by two-way ANOVA for repeated measures with factors time and dose (open-label chronic pain study) or injection drug (randomized, controlled chronic pain study, and postoperative pain study). Incidence of side effects was compared across doses or treatments by Chi-Square or Fisher exact test. Exploratory analyses were performed using Pearson correlation and linear regression. A value of $P<0.05$ was considered significant. "
Were all the subjects analysed in the groups to which they were randomly allocated (i.e. intention to treat analysis)?	Not reported	
Is the paper free of selective outcome reporting?	Yes	
For cross-over studies only		
Was this intervention suitable for a cross-over study?	Yes	Pain studies are complex in nature due to the heterogenous nature of pain. Cross-over was appropriate to detect the effectiveness of IT ketorolac, as all patients were controls for themselves. "Cross-over trials are suitable for evaluating interventions with a temporary effect in treatment of stable, chronic conditions" (Cochrane Handbook 16.4.2).
Was the washout period adequate?	Yes	The half life of IT ketorolac in young adults is 3.5 – 9.2 hrs (Wiki). Considering that the authors reported that "patients returned at least 1 week, but no more than 3 months later, for the crossover treatment", the washout period does seem adequate.
Other		
What is the overall risk of bias?	Low - Moderate	No allocation concealment was reported as well as blinding of the patients or investigators of the study to the drug. Attrition rate was also not reported.

Results.

The study included a total of 12 patients with a history of chronic pain (mean duration 12 ± 2 years) which had been previously receiving IT morphine for at least 6 weeks. "Both pain intensity (P = 0.01) and unpleasantness (P = 0.02) decreased with time after intrathecal injections, but there was no difference between ketorolac and saline (fig. 3), and there was no significant interaction between treatment and time." However it was not significantly different to when patients received placebo. Patients who experienced at least 30 or 50% pain relief following IT administration did not differ between saline and ketorolac groups. Statistical analysis with ANOVA revealed no significant interaction between treatment and time. There was no correlation, however, between intrathecal morphine daily dose and resting pain score, minimum pain score after ketorolac, average pain score after ketorolac, or summed pain intensity difference scores after ketorolac administration. Similarly, there was no correlation between intrathecal morphine daily dose and pain scores after intrathecal saline, or between intrathecal morphine daily dose and the difference in pain score after ketorolac and saline.

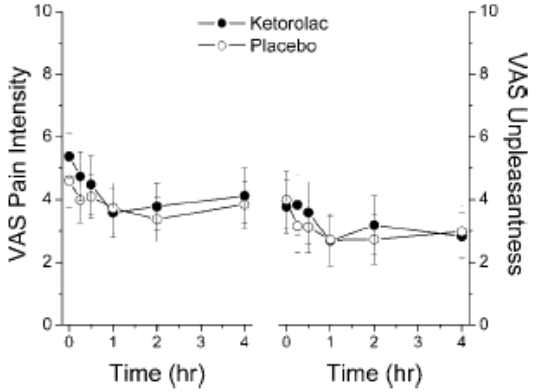
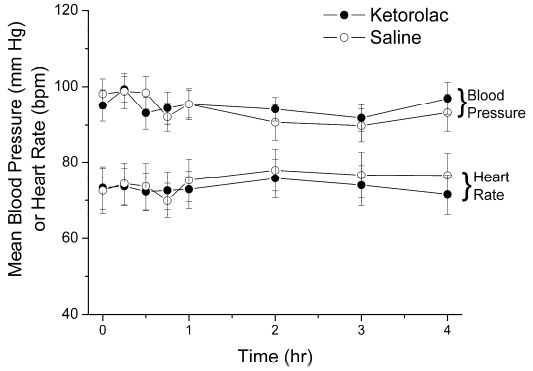


Fig. 3. Visual Analog Scale (VAS, in cm) pain intensity and unpleasantness before and after intrathecal ketorolac or saline injection, just after time 0, in patients in the randomized, controlled chronic pain study. Each symbol represents the mean ± SEM of 12 subjects. Groups do not differ by two-way repeated measures analysis of variance.



Supplemental Digital Content 5: Mean blood pressure and heart rate before and after intrathecal injection of ketorolac or saline (just after time 0) in patients in the randomized, controlled chronic pain study.
Each symbol represents the mean ± SEM of 12 subjects.
No significant change over time by one way repeated measures ANOVA.

Side effects

Statistical analysis on adverse events between patient groups did not reveal any differences. Ahead of IT saline or ketorolac administration, patients reported existing adverse events including headache (n = 5 before saline, n = 6 before ketorolac), lower extremity weakness (n = 6), anxiety (n = 2), nausea (n = 1) and sedation (n = 1). Following IT ketorolac adverse events included mild sedation lasting less than 2 hours (n = 2), mild dizziness lasting less than 2 hours (n = 1), hot sensation in the back, headache, urinary retention and hives (n = 1) 4 days after injection, lasting less than 4 hours. Following IT saline adverse events included mild sedation lasting less than 1 hr (n = 2), mild nausea lasting less than 1 hr (n = 2), mild headache lasting less than 2 hr (n = 1). Two serious adverse events occurred. One patient experienced a numb left leg for less than 2 h after intrathecal injection of saline, and, as noted, this subject's pump contained bupivacaine. One patient committed suicide 6 months after study.

Author's Conclusions.

"We failed to observe greater analgesia from intrathecal ketorolac than saline placebo in patients with primarily low back and lower extremity pain and a combination of somatic and neuropathic components".

"2 mg of intrathecal ketorolac was not associated with serious side effects, failed to reduce ongoing pain in chronic pain patients more than placebo….These observations are limited by the small number of subjects studied, and patient population, and the amount and timing of ketorolac dosing."

"Under the conditions of these studies, it seems that spinal cylcooxygenase activity does not contribute to chronic or postoperative pain."

Our Comments/Summary.

The allocation concealment was not reported in the study, potentially introducing into the results selection bias. Although the authors report that it was a randomised, controlled study, in which the IT solutions were prepared by "an individual not involved in the patient's care or research evaluation", they did not say whether the patient or person administered the drug to the patient were blinded. They did not comment on whether the solutions were similar in appearance etc or if both groups were treated similarly during the study. This does not give confidence in the accuracy of the true effect size and may have attributed to the non-significant difference in pain intensity between saline and ketorolac groups.

The study did not report the origin or pain syndrome of patients enrolled in the RCT, i.e. neuropathic or complex regional pain syndrome (CRPS) etc. This might have an impact on the response to pain reduction and should be investigated in further IT infusion studies. Patients were studied twice (cross-over study), hence they received placebo and ketorolac but at two alternative visits. A washout period of at least 1 week but no greater than 3 months was reported, suggesting some assurance of no direct placebo-ketorolac interactions which would modify the true effect size. However, it is unknown if the initial pain intensity and symptoms returned to test the efficacy of the second drug treatment, either saline or ketorolac.

The attrition rate seemed to be unaffected after the patient's second visit, however this could have been due to the financial incentive offered by the study authors. The attrition rate was not reported on by the authors at either visit.

The degree of error in the study was not reported on. It cannot be assumed that due to the study design the patients serve as their own controls and hence no error is present. Furthermore, the authors did not report if any test for normality had been conducted on the data before performing the ANOVA, hence it is difficult to know if the results followed a normal distribution or not. The confidence intervals were also not reported which is an effective means of determining any random error in the results of the study.

Interestingly, in the results the authors report "Two serious adverse events occurred. One patient experienced a numb left leg for less than 2 h after intrathecal injection of saline, and, as noted, this subject's pump contained bupivacaine. One patient committed suicide 6 months after study." However, we do not know if this was a result of the drug treatment or other factors, although the authors do state that "there was no significant interaction between treatment and time".

We contacted the author of the study to assess whether the groups were treated the same, if outcome measures were assessed independently and if the outcome assessors were blind to the intervention group, to which they stated a yes to all. The authors also commented, "That paper is more fundamental than practical, since there no longer exists a preservative free solution of ketorolac for spinal administration". This may suggest that other medications with a similar pain-relieving action should be utilised as agents used in IT with preservatives are toxic to the body and should be used in non-

cancer patients if they are at end of life (Deer, T et al, 2007).

The overall risk of bias was low-moderate with the authors not reporting on the allocation concealment or degree of error. However, overall the study revealed no greater pain relief with IT ketorolac and IT morphine in comparison to IT morphine and saline (control). Although the outcome measurements were subjective (patient-reported, VAS score and thermal threshold), in context of the field of study being pain, the evidence can be considered as positive.

Table A5.3 Critical appraisal table *(Teasell, R, 2010)*

Study: Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, Hsieh JT, Townson, AF, Short, C the Spinal Cord Injury Rehabilitation Evidence Research Team. A Systematic Review of Pharmacological Treatments of Pain After Spinal Cord Injury. Archives of physical medicine and rehabilitation. May 2010. 91 (5): 816-31

Description of study: Systematic review of RCTs (or other types of studies).

Patient/population	Patients with mixed pain (neuropathic and musculoskeletal/spastic) after spinal cord injury (SCI)
N	26 (IT studies only)
Setting	Not reported
Intervention/indicator	

Reference	Intervention
Siddall, P et al, 2000 RCT (n=8)	Each patient was randomised to either: 0.2-1mg of morphine, 50 to 100µg of clonidine or placebo; dosage increased if the subject had no side effects and no pain relief. Once each received satisfactory pain relief (or developed side effects from drug they were on), he or she was given a mixture of morphine and clonidine.
Uhle E et al, 2000	Subjects were implanted with an intrathecal pump, originally were given 3ml saline followed by 1ml morphine; this was followed by a second dose of morphine (0.02mg) provided that no side effects or benefits had been noted. This was followed by clonidine (30ug in 1ml); then, depending on side effects, a final dose of clonidine (50ug in 1ml).
Loubser, P and Akman, N, 1996	Baclofen infusion pump was implanted into SCI patients.

Comparison/control	IT saline (Siddall, P et al, 2000)
Outcomes	

Reference	Intervention
Siddall, P et al., 2000 (RCT, n=8)	1. The administration of morphine or clonidine resulted in a mean reduction in pain levels; however, this is not statistically significant compared with the effects of placebo. 2. When mixture of morphine and clonidine was administered, there was a significant reduction in pain vs. that achieved on placebo (P=0.008).
Uhle E et al, 2000	1. Subjects reported good to excellent pain reduction after clonidine administration. 2. After clonidine bolus, subjects experienced the optimum pain reduction. Average initial dose of

		clonidine was 53µg/d; this decreased (or stabilized) to 44µg/d.
	Loubser, P and Akman, N, 1996	1. 12/16 patients described chronic pain before procedure, experienced a reduction on VAS measuring severity of neuropathic pain at 6 and 12 months; however, this difference was not statistically significant (P=.26) 2. No significant differences were noted between VAS at the 6- and 12-month assessments after pump implantation. 3. For those with neuropathic pain symptoms, ANOVA revealed a non-significant effect of intrathecal baclofen on pain at both 6 and 12 months (P=.26). 4. In 5 of 6 patients with musculoskeletal pain symptoms, pain severity decreased in conjunction with control of spasticity. Musculoskeletal pain responded to baclofen infusion, while neuropathic pain did not.
Inclusion Criteria	• Studies were only included for analysis if at least 50% of subjects had an SCI, there were at least 3 subjects with an SCI, and there was a definable intervention being studied. Only studies published in the English language were included. • Studies examining all types of pain after SCI (nocioceptive, neuropathic, mixed) were examined	
Exclusion Criteria	Not reported	

Study Validity.

		Document evidence of this from the article (including quoting from the article). ***Add any other relevant comments, including if this is likely to influence the results of the study.***
Is it clear that there were no conflicts of interest in the writing or funding of this review?	Yes	Supported by Ontario Neurotrauma Fund (grant no. 2007-SCI-SCIRE-528), Rick Hansen Man in Motion Foundation (grant no. Rick Hansen 2008-13), and SCI Solutions Network (grant no. 2010-01). No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.
Does the review have a clearly- focused question?	Yes	To assess the research evidence of treatment approaches currently used in the pharmacologic management of pain in persons with SCI.

Is a systematic review the appropriate method to answer the question?	Yes	
Does the review have specified inclusion/exclusion criteria?	Yes	See above "The review included RCTs and non-RCTs, which included prospective controlled trials, cohort, case series, case-control, pre-post studies, and post studies. Case studies were included only when there were no other studies found"
If there were specified inclusion/ exclusion criteria, were these appropriate??	Yes	
Does the review document a comprehensive search strategy?	Yes	"A systematic review of all relevant literature, published from 1980 to June 2009, was conducted by using multiple databases (MEDLINE, CINAHL, EMBASE, PsycINFO). Key words included the following: pain, pain treatment, pharmacology, pain management, secondary complications, anticonvulsants, cannabinoids, antidepressants, medications, anesthetic, analgesic, and antispastic. Retrieved references were scanned for relevant citations that might have been missed by the searches of the various databases. "
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Were 2 or more independent reviewers used for: **4. application of inclusion criteria to assess eligibility of studies?**	Not reported	
5. extraction of data from study reports?	Not reported	
6. appraisal of study quality?	Yes	"A methodologic quality assessment was conducted for each article by 2 reviewers by using either the PEDro scoring[27] system for RCTs or the D&B tool[28] for non-randomized studies. Scoring discrepancies were resolved by a third blind reviewer."

Were the strengths and limitations of included studies and potential impact on the results discussed?	Yes	"Despite the fact that the total number of studies exploring pain management after SCI was small, over 70% of the studies reviewed were RCTs". "Most studies lacked evidence of numbers to treat and effect-size calculations." Whilst the VAS and McGill Pain Questionnaire have been "shown to be reliable and valid in the assessment of pain…neither has been specifically validated for the assessment of post-SCI pain". "Several of the studies reviewed were unblinded. One area of concern with unblinded studies is the patients' awareness that they were receiving the active medication, which likely biased their responses to the drug or their reporting of pain after SCI." "Most studies did not specify the type of neuropathic pain, and, hence, effectively evaluating treatments was not possible." "Intrathecal baclofen only reduces SCI pain when the pain is related to muscle spasms. There is a need for confirmatory research because of the small sample size and the lack of significant improvement in a later before-and-after trial"
Was the validity of included trials appraised using appropriate criteria?	Yes	"A methodologic quality assessment was conducted for each article by 2 reviewers by using either the PEDro scoring[27] system for RCTs or the D&B tool[28] for non-randomized studies. Scoring discrepancies were resolved by a third blind reviewer."
Is there a summary of the results of individual studies?	Yes	Tables 4 and 6
If meta-analyses were conducted, was it reasonable to do so?	N/A	
If meta-analyses were conducted, was it done appropriately?	N/A	
Other		
What is the overall risk of bias?	Low	

Results.

Pain reduction following IT drug administration

A total of 8 patients were initially randomised to receive placebo, morphine (0.2-1mg) or clonidine (50-100 µg) through implanted lumbar intrathecal pumps (Siddal et al, 2000). "Once a subject achieved satisfactory pain relief or suffered drug side effects with 1 of the 3 treatments, that subject was treated with a mixture of clonidine and morphine. Both morphine and clonidine given alone showed a trend toward pain reduction; however, when the combination of morphine and clonidine was administered, there was a significant reduction in pain (p=0.008)."

A total of eight patients (Uhle 2000) were implanted with pumps dispensing IT morphine (dose of 0.02mg) followed by IT clonidine (mean dose 44µg) in a prospective, controlled trial. Pain relief was measured by VAS scale, however no quantitative data was reported. The results of this study showed that patients reported good to excellent pain reduction after clonidine administration.

Similarly, a pre-post case series with a total of 12 patients with chronic pain (neuropathic and musculoskeletal) were implanted with pumps dispensing baclofen (dose not reported). VAS pain scale was recorded at 6 and 12 month periods, revealing a reduction in score at both time points, however using ANOVA this was not statistically significant (P = 0.26). A total of 5 out of 6 patients with musculoskeletal pain had decreased pain severity and control of spasticity.

The review also looked at the effectiveness of pain relief with oral medications (gabapentin/pregabalin, lamotrigine, levetiracetam, valproate, trazadone, amitriptyline, lidocaine, tramadol, cannabinoids, mexiletine and capsaicin) and intravenous medications (ketamine, alfentanil, and botulinum toxin) which were not part of our question.

Author's Conclusions.

"There is level 1 evidence from one RCT and level 2 evidence from a prospective controlled trial that a combination of intrathecal morphine and clonidine results in a significant reduction in neuropathic pain. There is level 4 evidence that intrathecal baclofen reduces musculoskeletal pain after SCI in conjunction with spasticity reduction."

Our Comments/Summary.

One of the limitations of the studies used in the review is that small sample sizes were utilised, hence the outcomes are less precise and may likely change with larger numbers. Funnel plots or sensitivity analysis could be useful in determining if any small-study effects are present.

Only low level evidence existed for intrathecal baclofen reducing pain after SCI in conjunction with spasticity reduction. Further high level studies need to be conducted to say with certainty that intrathecal baclofen has this effectiveness or not. The review did not report the quantitative changes in VAS pain scores, making it difficult to estimate the true effect size.

Due to the type of pain patients presented with in the studies being of a heterogenous nature, the generalisability is low. However, the overall level of bias in the review is low.

Table A5.4 Critical appraisal table *(Rauck, R, 2009)*

Study: Rauck, R, Wallace, M, Burton, A, Kapural, L, and North, J. Intrathecal Ziconotide for Neuropathic Pain: A Review. Pain Practice. 2009. 9 (5):303 327-337.	
Description of study: *Systematic review of RCTs (or other types of studies).*	
Patient/population	Patients with chronic severe (non-cancer) pain
N	n/a
Setting	Not reported
Intervention/indicator	**Reference** / **Intervention** Wermeling D et al, 2003 (open-label) n=22 / IT ziconotide (1-hour infusion, doses -1 mcg, n = 5; 5 mcg, n = 8; 7.5 mcg, n = 6; 10 mcg, n = 5) Taqi D et al, 2002 (open-label) n=25 / IT Ziconotide Kapural L et al, 2009 (case series) n=7 / IT ziconotide (n=3), IT combination therapy only (n=1), IT monotherapy followed by combination therapy (n=3). IT concomitant medications included – Bupivacaine with sufentanil, morphine, hydromorphone and clonidine with hydromorphone Saulino M et al, 2009 (case series) n=5 / IT Ziconotide with baclofen
Comparison/control	None
Outcomes	**Reference** / **Intervention** Wermeling D et al, 2003 (OL) / Ziconotide cerebrospinal fluid (CSF) concentrations, mean VASPI scores and adverse events Taqi D et al, 2002 (OL) / Mean VAS scores and adverse events Kapural L et al, 2009 (case series) / Mean VAS scores, functional outcomes and adverse events Saulino M et al, 2009 (case series) / VASPI scores, quality of life and functional outcomes, and adverse events.
Inclusion Criteria	• For clinical studies, both controlled (randomized or nonrandomized) and uncontrolled studies (case series or case reports) were included. • Patients with any type of neuropathic pain condition. Male and female patients of all ages and races/ethnicities were included. • IT administration of ziconotide for neuropathic pain, in any dose, alone or in conjunction with one or more drugs.

	• Pain assessment as an outcome measure
Exclusion Criteria	Not reported

Study Validity

		Document evidence of this from the article (including quoting from the article). ***Add any other relevant comments, including if this is likely to influence the results of the study.***
Is it clear that there were no conflicts of interest in the writing or funding of this review?	No	"Financial support for this review was provided by Elan Pharmaceuticals, Inc., and editorial support was provided by MedLogix Communications, LLC. Dr. Rauck is a paid consultant and a study investigator funded by Elan Pharmaceuticals, Inc. Dr. Wallace is a consultant for Elan Pharmaceuticals, Inc., and has received research support from Medtronic, Inc. Dr. Burton has received a research grant from Medtronic, Inc. Dr. Kapural and Dr. North are paid consultants for Elan Pharmaceuticals, Inc."
Does the review have a clearly- focused question?	Partial	"The purpose of this article is to review current information regarding the use of ziconotide in the treatment of neuropathic pain."
Is a systematic review the appropriate method to answer the question?	Yes	
Does the review have specified inclusion/exclusion criteria?	Yes	See above.
If there were specified inclusion/ exclusion criteria, were these appropriate??	Yes	

Does the review document a comprehensive search strategy?	Yes	"Relevant publications were identified through searches of all years of PubMed, EMBASE, CINAHL, Biological Abstracts, Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts. The search terms were: ziconotide, SNX-111, MVIIA, Prialt, and neuropathic pain. The reference lists of publications identified through electronic literature searches were searched manually for any additional relevant literature. In addition, association meetings that cover IT therapy topics were identified; abstracts from the following association meetings were searched (years were determined on the basis of the online availability of published abstracts as of January 27, 2009): American Academy of Pain Medicine (2001 to 2008), North American Neuromodulation Society (2006 to 2007), and American Pain Society (2003 to 2008). All searches were limited to the English language."
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Were 2 or more independent reviewers used for: **7. application of inclusion criteria to assess eligibility of studies?**	Not reported	
8. extraction of data from study reports?	Not reported	
9. appraisal of study quality?	Not reported	
Were the strengths and limitations of included studies and potential impact on the results discussed?	Partial	"Results from the 2 DBPC ziconotide trials that used high starting doses and rapid dose escalation indicated that neurological AEs were reversible with a ziconotide dose decrease or discontinuation". "For the several case studies presented in this review, there is a possibility for self-selection bias because patients with a very favorable response to ziconotide may be more likely to be reported. Other limiting factors include the variable therapeutic window of ziconotide and the severity of AEs reported with ziconotide." "Because of the variety of measurement tools used in pain studies, these data were not extracted or evaluated in this review."
Was the validity of included trials appraised using appropriate criteria?	Not reported	

Is there a summary of the results of individual studies?	Yes	
If meta-analyses were conducted, was it reasonable to do so?	N/A	
If meta-analyses were conducted, was it done appropriately?	N/A	
Other		
What is the overall risk of bias?	Insufficient information	

Results.

Open-label studies

Wermeling, 2003

A total of 22 patients received a 1 hour IT infusion of ziconotide. "Ziconotide cerebrospinal fluid (CSF) concentrations were found to be significantly ($P < 0.05$) positively correlated with efficacy measures, including VASPI score differences, summed pain intensity differences, and total pain relief scores." Furthermore, ziconotide CSF concentrations were found to be significantly ($P < 0.05$) positively correlated with the incidence of both all AEs and nervous system-related AEs. "The most commonly reported nervous system-related AEs were dizziness, somnolence, paresthesia, and abnormal gait. Ziconotide doses were found to be significantly ($P < 0.05$) positively correlated with the incidence of both all AEs and non-nervous system-related AEs. The most commonly reported non-nervous system-related AEs were nausea, headache, and amblyopia."

Taqi, 2002

In another open-label study 25 patients received IT ziconotide for at least 3 months. "Most patients (72.0%) reported improved analgesia with low doses of ziconotide; however, many patients discontinued ziconotide because of AEs associated with upward titration. All patients were switched to IT opioid therapy; 21 of 25 patients (84.0%) reported they would like to have ziconotide added to their IT opioid regimen."

Case series

Kapural, 2009

Out of 7 patients in the case series, mean VAS scores changed by 52% (89.3mm decreased to 42.9mm). "Two patients had substantial improvements in pain and/or functionality with ziconotide therapy." After treatment with ziconotide, 3 patients were able to discontinue all IT medications; 2 of these patients were pain free at their last assessment, and the remaining patient required only intermittent oral oxycodone

to manage pain.

Two other patients had substantial improvements in pain and/or functionality with ziconotide therapy. For each patient in whom edema and skin discoloration were noted (3 of 7 cases), these symptoms resolved or substantially improved during the course of ziconotide therapy. “All but 1 of the patients in these case studies experienced AEs. The majority of AEs were neuropsychiatric or cognitive in nature”. “AEs included urinary retention, depression, anxiety, and hallucinations; urinary retention was reported 5 times in 4 patients”. One patient with CRPS type II, who had an aggressive ziconotide titration regimen, experienced severe neuropsychiatric AEs that eventually led to drug discontinuation.

Saulino, 2008

VASPI scores improved from baseline by a mean of 50.3% (range, 33.3% to 75.0%). The mean time to onset of pain relief was 15 weeks (range, 7 to 26 weeks), with a corresponding mean ziconotide dose of 3.7 mcg/day (range, 1.3 to 8.1 mcg/day).

All 5 patients had improvements in activities of daily living and/or in quality of life. One patient had SAEs of nausea, vomiting, and dehydration; these SAEs were not considered related to ziconotide and resolved with treatment.

Author’s Conclusions.

“Evidence from case studies, case series, open-label studies, and DBPC trials suggests that ziconotide, as either monotherapy or in combination with other IT agents, can be effective in treating patients who have refractory neuropathic pain”.

“Additional studies evaluating the long-term efficacy and safety of ziconotide for neuropathic pain may be warranted”.

Our Comments/Summary.

There is a low risk of bias in relation to the financial support the authors were provided by Elan Pharmaceutical, Inc. All authors are receiving support from pharmaceutical companies that produce IT ziconotide and the infusion pumps, “the study investigator is funded by Elan Pharmaceuticals, Inc. Dr. Wallace is a consultant for Elan Pharmaceuticals, Inc., and has received research support from Medtronic, Inc. Dr. Burton has received a research grant from Medtronic, Inc. Dr. Kapural and Dr. North are paid consultants for Elan Pharmaceuticals, Inc.” This is likely to impact on the presentation and reporting of results from studies conducted on IT ziconotide for neuropathic pain.

One study that conducted a meta-analysis (Collins et al, 2005) could not be appraised as it included a study (Staats, 2004) that used patients with cancer or AIDS and combined the results with another two studies (Rauck, 2006 and Wallace, 2006) which did not have patients of this type, which was an exclusion criteria of the committee for this evidence review.

There is very little information in this paper in regards to the methods undertaken. Assessment of the quality of the studies included in the paper is not reported and there is no reference to any supplemental papers that may contain this information.

There is insufficient information to assess the quality of this paper and to determine the risk of bias

Note – The study included titled Saulino, M et al, 2009 is the same study in the Wallace critical appraisal dated as 2008.

Table A5.5 Critical appraisal table *(Wallace, M, 2010)*

Study: Wallace, M, Rauck, R and Deer, T. Ziconotide Combination Intrathecal Therapy: Rationale and Evidence. Clinical Journal of Pain. September 2010. 26 (7): 635-644.	
Description of study: *Systematic review of RCTs (or other types of studies).*	
Patient/population	Patients with chronic pain
N	114 (8 studies) **Please note all these studies may not have assessed our outcomes of interest.**
Setting	Not reported
Intervention/indicator	

Reference	**Intervention**
Webster, L et al, 2008	IT morphine (average dose Titration: 0.25–1.25 mg/d; Extension: 0–2.1 mg/d morphine with IT ziconotide (average dose 4.8-24.20 mcg/d)
Wallace, M et al, 2008	IT morphine (5.7-13.0 mg/d) with IT ziconotide (Titration: 0.60–7.20 mcg/d; Extension: 0.84-4.20 mcg/d)
Madaris, L et al, 2008	IT morphine (0.5-1.5 mg/d) with IT ziconotide (0.5-4.5 mcg/d)
Saulino, M et al, 2007	IT hydromorphone (0.44 mcg/d-1.32 mg/d) with ITZ (2.4-11.0 mcg/d)
Saulino M et al, 2008	IT baclofen (62-500 mcg/d) with ITZ (1.2-16.0 mcg/d)
Deer, T, 2009 *(short study, not long-term)*	IT Hydromorphone, 4.6 mg/d#; morphine, 5.2 mg/d#;fentanyl, 990 mcg/d#; sufentanil, 1100 mcg/d#; bupivacaine, 0.5 mg/d#; clonidine, 113 mcg/d#; baclofen, 14 mcg/d with ITZ (Start: 0.5 mcg/d; Week 12: 0.6-5.7 mcg/d)
Krakovsky A and Bowie E, 2007	N/A *(abstract only)*
Stanton-Hicks M and Kapural, 2006	ITZ (0.5-24.0 mcg/d) with IT N/A

Comparison/control	As studies were observational, no comparison/control
Outcomes	

Reference	**Intervention**
Webster, L et al, 2008	VASPI: 26.3% improvement

		AEs: dizziness, peripheral edema, pruritus, nausea
	Wallace, M et al, 2008	VASPI: 14.5% improvement AEs: confusion, dizziness, abnormal gait, hallucinations, anxiety
	Madaris, L et al, 2008	Pain score: 20%-60% improvement AEs: none
	Saulino, M et al, 2007	VASPI: 85%-90.0% improvement AE: increased intermittent catheterization
	Saulino M et al, 2008	VASPI: improvement of 30.0%-75.0% AEs: nausea and vomiting with dehydration; sedation, urinary hesitancy, loss of bladder control, and anorexia
	Deer, T, 2009 *(short study, not long-term)*	VAS: 20% of patients experienced substantial improvements in analgesia AEs: increased pain and depression in 1 patient
	Krakovsky A and Bowie E, 2007	83.8% of patients reported an improved pain score (range of improvement, 10%-50%) AEs: none
	Stanton-Hicks M and Kapural, L, 2006	VAS: 50.0% improvement from before starting ziconotide treatment to last available assessment AEs: none
Inclusion Criteria	Not reported	
Exclusion Criteria	Not reported	
Study Validity		
		Document evidence of this from the article (including quoting from the article). ***Add any other relevant comments, including if this is likely to influence the results of the study.***
Is it clear that there were no conflicts of interest in the writing	No	"Financial support for this project was provided by Elan Pharmaceuticals, Inc. MedLogix Communications, LLC, provided editorial support for this project".

or funding of this review?		
Does the review have a clearly-focused question?	Yes	"This review summarizes and evaluates the publications from preclinical and clinical peer-reviewed experiments that have investigated the safety and effectiveness of ziconotide in combination with a variety of other drugs." *(Note - does not mention the population though)*
Is a systematic review the appropriate method to answer the question?	Yes	
Does the review have specified inclusion/exclusion criteria?	No	
If there were specified inclusion/ exclusion criteria, were these appropriate??	N/A	
Does the review document a comprehensive search strategy?	Partial	"The PubMed, EMBASE, and Cumulative Index to Nursing and Allied Health Literature databases were searched without any restrictions. These combined search terms were used: ziconotide, PRIALT, MVIIA, or SNX-111 and combination, morphine, hydromorphone, bupivacaine, baclofen, clonidine, fentanyl, or sufentanil. In addition, association meetings that cover IT therapy topics were identified; only those meetings with published abstracts were included. Abstracts from these association meetings were searched (years were determined on the basis of the availability of published abstracts as of January 27, 2009): American Academy of Pain Medicine (2001 to 2008), North American Neuromodulation Society (2006 to 2007), and American Pain Society (2003 to 2008)".
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Were 2 or more independent reviewers used for:	Not reported	.

10. application of inclusion criteria to assess eligibility of studies?		
11. extraction of data from study reports?	Not reported	
12. appraisal of study quality?	Not reported	
Were the strengths and limitations of included studies and potential impact on the results discussed?	No	
Was the validity of included trials appraised using appropriate criteria?	Not reported	
Is there a summary of the results of individual studies?	Yes	
If meta-analyses were conducted, was it reasonable to do so?	N/A	
If meta-analyses were conducted, was it done appropriately?	N/A	
Other		
What is the overall risk of bias?	Insufficient information	

Results.

5 studies used, n = 111

Webster, 2008

An open-label study involving 25 patients showed that IT morphine with ziconotide revealed mean VASPI scores improved by 26.3% from baseline (titration phase). "On the Categorical Pain Relief Scale (CPRS), 17 of 25 patients (68.0%) reported ''moderate'' or ''a lot'' of pain improvement at the end of the titration phase, and 14 of 18 patients (77.8%) reported this level of pain improvement at the extension phase termination visit. Additional pain relief was reported on the Clinical Global Impression (CGI) scale by 23 of 25 patients (92.0%) at the end of the titration phase and by 15 of 17 patients (88.2%) at the extension revealed that ''good,'' ''very good,'' or ''excellent'' overall pain control was reported by 17 of 25 patients (68.0%) at the end of the titration phase and by 14 of 19 patients (73.7%) at the extension phase termination visit."

"The most common (occurring in Z10% of patients in either study phase) treatment-emergent AEs considered to be related to the study drugs were dizziness (titration phase, 28.0%; extension phase, 4.2%), peripheral edema (titration phase, 12.0%; extension phase, 12.5%), pruritus (titration phase, 24.0%; extension phase, 0%), and nausea titration phase, 16.0%; extension phase, 4.2%). No unexpected AEs were reported, and no serious treatment-emergent AEs that were considered to be related to the study drugs were reported."

Wallace, 2008

Another open-label study involving 25 patients which similarly utilised IT morphine with ziconotide (different doses – see table on page 1), 14 out of 25 (56%) reported ''slight'' to ''complete'' improvement in pain relief on the CPRS. "Improved pain relief on the CGI scale was reported by 17 of 25 patients (68.0%) at the end of the titration phase and by 11 of 17 patients (64.7%) at the extension phase termination visit. Results from the CGI scale revealed that ''good,'' ''very good,'' or ''excellent'' overall pain control was reported by 8 of 25 patients (32.0%) at the end of the titration phase and by 6 of 17 patients (35.3%) at the extension phase termination visit."

"The most common (occurring in Z15% of patients in either study phase) treatment-emergent AEs considered to be related to the study drugs were confusion (titration phase, 30.8%; extension phase, 16.7%), dizziness (titration phase, 26.9%; extension phase, 11.1%), abnormal gait (titration phase, 23.1%; extension phase, 5.6%), hallucinations (titration phase, 11.5%; extension phase, 16.7%), and anxiety (titration phase, 7.7%; extension phase, 16.7%). Creatine kinase levels >3 times the upper limit of normal were recorded for 5 patients during the titration phase and by 6 patients during the extension phase."

Saulino, 2008

A case series of 5 patients administered IT baclofen with the addition of IT ziconotide showed an improvement in VASPI scores by an "average of 50.3% from baseline to last assessment. Adverse events were reported by 1 patient (nausea and vomiting with dehydration), but these AEs were considered unrelated to ziconotide treatment. The patient was hospitalized for 5 days, and the AEs resolved after rehydration and a reduction of the patient's transdermal fentanyl dose." Two patients also had IT treatment, but the addition of baclofen to IT ziconotide.

Deer, 2009

In a retrospective observational study a total of 16 patients received IT ziconotide with concomitant IT opioids - hydromorphone (n=7), morphine (n=5), fentanyl (n=3), and sufentanil (n=1); other adjunctive IT

drugs were bupivacaine (n=4), clonidine (n=3), and baclofen (n=1). “One patient reported increased pain and depression 2 weeks after the initiation of ziconotide therapy. Ziconotide therapy was discontinued, and the patient received treatment for depression. All AEs resolved in this patient over a 4-week period. No other AEs were reported by this or any other patient. Among the 15 patients who completed 12 weeks of ziconotide combination therapy, 3 (20.0%) reported substantial pain relief, 10 (66.7%) reported no to moderate pain relief, and 2 (13.3%) reported increased pain.”

Krakovsky and Bowie, 2007

Another respective observational study involving a total 37 patients involved IT ziconotide with concomitant IT drugs (information not given). Of the 37 patients, “31 patients (83.8%) experienced improved analgesia (range of improvement, 10% to 50%; no data were provided for the remaining 6 patients), 9 patients (24.3%) reported increased activity, 4 patients (10.8%) decreased their IT opioid dose, 5 patients (13.5%) decreased their IT adjuvant drug dose(s) (bupivacaine and clonidine), and 6 patients (16.2%) decreased their oral opioid dose(s). No AEs were reported.”

TABLE 2. Ziconotide Combination Therapy: Summary of Clinical Data

Drug Combined With Ziconotide	Concomitant IT Drug Dose(s)	N	Duration	Ziconotide Dose	Key Points
Morphine	Titration: 0.25–1.25 mg/d*; Extension: 0–2.1 mg/d*[19]	25	76 wk	4.8-24.20 mcg/d*	VASPI: 26.3% improvement† AEs: dizziness, peripheral edema, pruritus, nausea‡
	5.7-13.0 mg/d*[20]	26	77 wk	Titration: 0.60–7.20 mcg/d; Extension: 0.84-4.20 mcg/d*	VASPI: 14.5% improvement† AEs: confusion, dizziness, abnormal gait, hallucinations, anxiety§
	0.5-1.5 mg/d[14]	1	6 mo	0.5-4.5 mcg/d	Pain score: 20%-60% improvement AEs: none
Hydromorphone	0.44 mcg/d-1.32 mg/d[15]	1	15 mo	2.4-11.0 mcg/d	VASPI: 85%-90.0% improvement‖ AE: increased intermittent catheterization
Baclofen	62-500 mcg/d¶‖[16]	7	8-104 wk	1.2-16.0 mcg/d	VASPI: improvement of 30.0%-75.0% AEs: nausea and vomiting with dehydration; sedation, urinary hesitancy, loss of bladder control, and anorexia
Multiple drugs	Hydromorphone, 4.6 mg/d# Morphine, 5.2 mg/d# Fentanyl, 990 mcg/d# Sufentanil, 1100 mcg/d# Bupivacaine, 0.5 mg/d# Clonidine, 113 mcg/d# Baclofen, 14 mcg/d#	16	12 wk	Start: 0.5 mcg/d; Week 12: 0.6-5.7 mcg/d	VAS: 20% of patients experienced substantial improvements in analgesia AEs: increased pain and depression in 1 patient
	NA[21]	37	NA	NA	83.8% of patients reported an improved pain score (range of improvement, 10%-50%) AEs: none
	NA[22]	1	NA	0.5-24.0 mcg/d	VAS: 50.0% improvement** AEs: none

*Median doses.
†Mean improvement at the end of the titration phase.
‡The most common (occurring in ≥10% of patients in either study phase) study drug–related treatment-emergent AEs.
§The most common (occurring in ≥15% of patients in either study phase) study drug–related treatment-emergent AEs.
‖Improvement in the patient's below-level spinal cord injury pain from before the initiation of ziconotide treatment to the last reported assessment.
¶Stable doses.
#Mean dose; T. Deer, MD, unpublished data, March 2009.
**VAS score improvement from before starting ziconotide treatment to last available assessment.
AE indicates adverse event; IT, intrathecal; NA, not available; VAS, visual analog scale; VASPI, visual analog scale of pain intensity.

The review also reported on pre-clinical outcomes following IT ziconotide with other drugs, however this was not part of our question.

Author's Conclusions.

"On the basis of the literature evaluated in this review, it is evident that ziconotide in combination with other IT drugs has been studied more extensively in preclinical investigations than in clinical

investigations. It is important to note that the effects of drugs in animal models do not always accurately reflect the effects of those drugs in humans."

"Although there are only a limited number of studies that have evaluated ziconotide when used in combination with other IT drugs, ziconotide is used as combination therapy in clinical practice.14–16 Therefore, clinicians must balance the lack of evidence-based data with their own clinical expertise and experience with ziconotide and other IT agents when designing IT therapy regimens. There is a need for additional evidence-based investigations of ziconotide combination therapies, including long-term clinical trials."

Our Comments/Summary.

There is very little information in this paper in regards to the methods undertaken. Assessment of the quality of the studies included in the paper is not reported and there is no reference to any supplemental papers that may contain this information.

One of the retrospective observational studies (Krakovsky and Bowie, 2007) reported that patients received IT ziconotide with other IT drugs, however they did not mention which drugs these were or what doses were given. No adverse events were reported, but the authors of the review did not report if they had contacted the study authors to confirm this observation from their only available publication of the study as an abstract.

The authors of the review did not report the true effect size for IT ziconotide with morphine or baclofen to observe if one treatment was more effective than the other.

Multiple drugs combined with IT ziconotide were studied in small sample sizes (n = 16, Deer, 2009) and for short time periods (12 wks, duration unknown for Krakovsky and Bowie, 2007). The number of adverse events may be increased if the study were longer in duration.

There is insufficient information to assess the quality of this paper and to determine the risk of bias.