NHS England

Evidence Review:

Ziconotide (intrathecal delivery) for chronic refractory cancer pain

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Contents

1. Introduction

Cancer pain is often very complex, and the most intractable pain is often neuropathic in origin, arising from tumour invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Surgery, chemotherapy and radiotherapy are cancer treatments that can cause persistent pain in cancer survivors, up to 50% of whom may experience persistent pain that adversely affects their quality of life.

First line drug treatment includes analgesics (e.g. paracetamol, NSAIDs and opioids), or for neuropathic pain, specific antidepressants and anticonvulsants. However, clinicians estimate that 20% of patients on oral drug administration fail to achieve adequate and sustained pain relief, and this figure is similar for other systemic routes of drug administration (transdermal or parenteral). When pain relief is insufficient or side effects are intolerable from systemically administered analgesics, increasingly invasive strategies can be used. These advanced interventional approaches include nerve blocks, surgery or intrathecal injection of drugs such as morphine, hydromorphone, fentanyl, clonidine or local anaesthetics (bupivacaine), given alone or in combination.

A novel biological approach for pain management is the intrathecal infusion of ziconotide in chronic, intractable pain management for patients who are intolerant or whose pain is refractory to first line therapies including the more commonly used intrathecal drugs such as morphine. Ziconotide does not lead to the development of addiction and tolerance and therefore represents a beneficial treatment option in patient groups requiring long-term pain management. In addition, intrathecal ziconotide avoids the risk of granuloma formation (at site of delivery) and subsequent risk of neurological deficit.

Currently, NHS England routinely commissions intrathecal pumps (for intrathecal drug delivery) in severe cancer pain only and not chronic non-cancer pain. Additionally, the current commissioning position for severe cancer pain only commissions morphine (and other opioid-based medications) and baclofen, not ziconotide. This policy addresses the use of ziconotide for the treatment of chronic refractory cancer pain.

2. Summary of results

Summary

There are over 30 publications reporting on the efficacy, or safety (or both) of intrathecal ziconotide. Much of this evidence base comes from cohorts or case series, with patient numbers commonly ranging from around 15 to 80, although there are also three randomised controlled trials (RCTs) and some larger cohort studies. Patient selection criteria vary between the studies, with common groups included being those with chronic pain following failed back surgery and other neuropathic pain. There are a smaller numbers of studies looking at shorter term impact on patients with cancer-related pain. There are some well-designed studies, but much of the evidence is limited by small size of studies, heterogeneity of patients selected, or use of concurrent medications. In addition, as a range of tools are used to try to assess the measurement of pain, this provides a further challenge to the assimilation of evidence across disparate studies.

Overall, the evidence (reviewed in detail below) indicates that use of IT ziconotide has a positive impact on severe and refractory pain (particularly as measured by improvements in mean Visual Analogue Pain Intensity scale (VASPI) scores) in those who respond positively. However, the precise clinical significance of this change is hard to fully interpret. There are some data showing early responders to ziconotide can sustain this efficacy but good long-term efficacy data is limited, in large part due to a high discontinuation rate of ziconotide over time. Studies, almost invariably, show a high rate of adverse events (AEs), commonly neurologic or psychiatric (including dizziness, confusion, and memory impairment) or visual disturbances, urinary retention, nausea and vomiting.

Detailed review

Is ziconotide via intrathecal drug delivery clinically effective and safe to use in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?

Two RCTs looked at the short term impact (less than two weeks) of ziconotide among patients mainly with non-

malignant (Wallace, 2006) or cancer and/or AIDs diagnoses (Staats, 2004). Wallace et al randomised patients with pain duration of over one year to IT ziconotide (169 patients) or placebo (86 patients), most of whom were on oral opioids at baseline. Patient eligibility for the study required a baseline VASPI score of at least 50, and the primary endpoint was set at a minimum 30% change in mean VASPI score after the initial titration period (6 days). The study results showed a 31.2% improvement in mean VASPI score from baseline in the ziconotide, which was significantly ($p<0.001$) different from the placebo group's mean change of 6.0%. Statistically significant improvements versus placebo were also seen in the ziconotide group in terms of secondary measures (e.g. Global McGill Pain Score (23% versus 9.2%)). However, the 95% confidence range for those with compete data ranged from 24.4-37.9%.

Although the authors conclude that ziconotide demonstrated efficacy, the wide confidence intervals raise questions. It seems that patients who did respond to ziconotide received an appreciable amount of pain relief (62% mean improvement in VASPI score), but this improvement was not consistent across the entire study population and is not generalisable. The dosing schedule was changed in response to high numbers of AEs and further limits this study. The most common SAEs in the ziconotide group were: dizziness, confusion, urinary retention, nausea and vomiting, amblyopia or visual abnormalities, abnormal gait, stupor or somnolence, ataxia or vestibular disorders, and encephalopathy. Overall, this study shows equivocal efficacy results and the potential for adverse events and the narrow therapeutic window with IT ziconotide. Major limitations of the study design include the change in dosing methodology mid-trial and the short duration of the trial, weakening the strength of evidence provided by this RCT.

Staats et al (2004) carried out a well powered (n=111, 96% power, 5% significance level, 30% change in VASPI scores between the two study groups), randomised, double-blind, controlled trial of IT ziconotide in cancer and AIDS patients with chronic, refractory pain (VASPI scores of at least 50 at baseline measurement). Primary endpoint results analysed for the "evaluable" population showed a significant difference between the ziconotide and placebo group in terms of mean VASPI improvement (ziconotide: 53.1% (95% CI 44-62.2%) versus placebo 18.1% (95% CI 4.8-31.4%)) with $p <0.001$ within the two weeks of the study. Additionally, moderate to complete pain relief was reported significantly more in the ziconotide group than in the placebo group (52.9% versus 17.5%, $p<0.001$). The ITT analysis also revealed a significant difference in mean VASPI score improvement between the ziconotide (51.4%) and placebo groups (18.1%) (95% CI 17.3-49.4%, $p<0.001$). A statistically significant difference in the percentage of patients responding (defined as a 30% improvement in VASPI score, without an increased dose or change in type of concomitant opioid) to the randomised treatment was seen, as well (ziconotide 50% versus 17.5% placebo, $p = 0.001$).

Ziconotide responders then entered a maintenance phase (n = 48, change in VASPI scores of 69.2%) and seemed to sustain efficacy through that period (end phase change in VASPI scores of 69.4%). However, statistical significance was not reported. The study protocol was changed after the first 48 patients were evaluated for safety in order to decrease the ziconotide dosing (0.1 µg/h or less to start, dose increased once per 24 hours until pain control or 2.4 µg/h is reached). Compared with placebo, ziconotide was associated with a larger number of (typically dose-related) adverse events: abnormal gait, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea, and vomiting.

The main limitations of this study are the short duration, and the protocol dosing change mid-trial Overall, this is a RCT of significant power which reached its primary end point, but the study's limitations weaken the potential strength of the evidence.

Other studies have used longer follow-up periods. Rauck (2006) reported on 220 patients in a randomised, double-blind, placebo-controlled trial of IT ziconotide. The study was well powered (80%, 110 patients, 39.5% standard deviation, 5% level of significance) for a 15% change in the mean VASPI score at week 3 (versus baseline). Patients had chronic, severe, refractory pain that was mostly neuropathic in origin and 90% had prior IT morphine.

Although the primary end point was reached, the clinical significance of this is not as clear. The study's primary end point analysis demonstrated a significant ($P = 0.036$) mean change in VASPI score from baseline with ziconotide treatment (14.7%) versus placebo (7.2%) at 3 weeks. However, the authors had pre-determined the definition of "responders" as patients showing a 30% change in VASPI score from baseline, and the mean VASPI change from baseline in the ziconotide group was only 14.7%. Results also revealed no statistically significant difference in other secondary measures (e.g. CPRS scores) or the mean decrease in opioid use (23.7% Z vs 17.3% Pl, $p=0.44$).

During the treatment phase of the study, there was a significantly higher rate of AEs in the ziconotide group (92.9% Z vs 82.4% Pl, p=0.023), however most AEs were mild or moderate (83.6% Z, 83.8% Pl). There was no significant difference in the SAEs reported during the treatment phase (11.6%, 19 SAEs Z vs 9.3%, 25 SAEs Pl, p=0.57), and only 1.8% (2/112) of patients in the ziconotide group had a treatment-related SAE (vs 1.9%, 2/108, in the placebo group). The study noted an AE profile that included chest pain, hypertension, ataxia, dizziness, and neuralgia.

Wallace (2010) carried out a qualitative systematic review of the published evidence relating to IT ziconotide in combination with other therapies (including morphine, clonidine and other agents). Due to the small size and heterogeneity of the source studies, no firm conclusions were drawn.

There have been two larger cohort studies: Ellis, 2008 (155 patients) and Wallace, 2008 (650 patients). Ellis (2008) was an open-label cohort study of 155 patients enrolled after responding to previous IT ziconotide in one of two study trials (both previous trials are reviewed separately in this evidence review, Staats 2004 and Wallace 2006). Efficacy outcomes revealed a 36.9% (SE 3.43) improvement in mean VASPI score from baseline until the last assessment ($p<0.0001$, n=144), and 45.8% (SE 6.8) mean change from baseline VASPI in the population remaining at 12 months ($p<0.0001$, n=31). Ziconotide-related AEs were experienced in 147 of 155 patients (usually mild or moderate in severity and reversible with dose decrease or discontinuation), and 31 patients had at least one SAE thought at least possibly related to ziconotide. No late-occurring AEs were noted. Limitations of the study include the open-label, non-randomised design, lack of control or direct comparison group, a high attrition rate, and selection bias introduced (patients had already been observed to be "responders" to ziconotide in one of two previous trials).

Wallace, 2008, reported on a large (n=644), open-label cohort study which aimed to evaluate the safety of IT ziconotide. Results showed 99.7% of participants with an AE and a high discontinuation rate due to AEs (61%, with 48.9% permanently discontinuing ziconotide due to AEs). Only 18.5% (119 patients) had 360 days of ziconotide in this study (the study median duration was 67.5 days), with AE being the main reason for discontinuation (followed by lack of efficacy in 29.7% and transition into another trial in 10.6%). AEs included nausea (52.6%), dizziness (51.6%), headache (40.1%), confusion (35.1%), pain (32.0%), somnolence (29.3%) and memory impairment (27.8%). Most reported AEs were described as either mild (43.5%) or moderate (42.3%), and more than half (58.6%) were considered unrelated to ziconotide. Those AEs considered ziconotide-related with the highest incidence were dizziness, nausea, confusion, memory impairment, and nystagmus. In terms of efficacy, 32.7% of participants with a baseline VASPI score of 50 or more (85.2%) had at least a 30% improvement at month one. Improvement in pain impact on daily life scores was also seen in 35.1% at month 2 ($P<0.001$). Study limitations include the relatively short duration for a comprehensive safety report, lack of comparator or control arm and the non-randomised, open-label design.

The rest of the main evidence derives from seven smaller cohort or case-control studies. Raffaeli (2011) undertook a retrospective cohort study of 104 patients enrolled in an Italian registry for IT ziconotide use of whom 51% had neuropathic pain and 53% of patients were given ziconotide as their first-line IT therapy. The results showed a >30% improvement in pain intensity in 72 of the 104 patients, and 45 of these patients had maintained the study drug and efficacy for over six months. This sustained result was statistically significant ($p<0.01$) and no differences in the change in Visual Analogue Scores (VAS) were noted by diagnosis. Similar AE were seen as in previous studies. Key limitations of the study include the retrospective observational and non-controlled design, a lack of standardisation in treatment protocol and data collection, and missing data.

Ver Donck (2008) led an open-label cohort study of 71 patients for which IT ziconotide was initially titrated. The duration of the titration phase was altered twice from the initial study methodology plans, first to accommodate local practice, then in response to a high rate of meningitis diagnoses. The authors also note that the study was initially designed for a larger population, but enrolment rates were not able to fulfil the initial set criteria. Approximately 90% of patients experienced AEs (363 AEs), with 33.8% of severe intensity and teo AEs reported in 10% or more of patients (dizziness 31% and nausea 14%). 26.8% of patients had an SAE, with 1 SAE being ziconotide-related (asthenia/leg weakness). Despite 52% with "moderate to complete pain relief" (per CPRS) and "good to excellent pain control" in 53.6% (per the CGI), only 10% reported complete satisfaction (per CGI), and only 62.3% were "at least somewhat satisfied." Median percent change in opioid dose was unchanged from baseline at week 4. The median percent change in VASPI scores showed significant improvement at weeks 1-4 (week 1: 11%, week 2: 32.6%, week 3: 31%, week 4: 23.5).

Webster (2009) reported on an open-label, long-term (133.4 patient-years), cohort extension study of IT ziconotide in 78 patients who had completed one of two prior studies (Wallace 2008, Ellis 2008, both

independently reviewed in this evidence review), where only 43% completed the study with others transferring to another trial, withdrawing consent or otherwise discontinuing. 71 of 78 patients had new AEs, with 37 (52%) considered ziconotide-related and 50 (70.4%) considered severe in intensity. Efficacy results showed no significant loss of pain control (per change in mean VASPI scores) over time, however there were only two points (days 600 and 960) where a >30% improvement in mean VASPI scores from the baseline in the study of origin were noted (a >10% mean improvement was noted otherwise, except for the Day 60 time point). This study is mainly limited by its post-trial, open-label, non-randomised, uncontrolled, non-comparative study design.

Dupoiron (2012) carried out a non-randomised, observational study of 77 patients assessing the safety of combined IT ziconotide, morphine, ropivacaine, and clonidine in patients with chronic cancer pain. There two major limitations to this study are the non-randomised, observational study design, and the use of four study medications together limiting the ability to determine a causal effect between outcomes and any one of the four new medications. Additionally, the patients had various forms of cancer (though a notable 19.5% had pancreatic cancer), and the percentage of patients with neuropathic versus other forms of pain was not reported.

The study results showed a significant improvement in pain intensity (numerical scale) from baseline after 15, 30, 60, and 90 days of IT therapy. However, the study does not definitively provide cause-effect evidence for ziconotide outcomes given the concomitant dosing of four other new IT medications, nor is there any evidence reported regarding use of ziconotide in first line presented in the publication.

Backryd (2015), Mohammed (2013), and Alicino (2012) are three smaller cohort studies enrolling 23, 20 and 20 patients respectively. They do not add additional information to that summarised above but were reviewed as part of this rapid evidence review.

Overall, there is some evidence supporting the efficacy of IT ziconotide in severe, refractory chronic pain. However, the evidence derives from studies with considerable methodological challenges, thus limiting its generalisability. It is clear that many patients experience adverse effects and for a substantial proportion, this is significant enough for them to cease treatment. However, the evidence implies there may be un-defined subgroups who derive much greater benefit.

Is Ziconotide via intrathecal drug delivery cost effective in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?

There is one publication reporting on the cost-effectiveness of ziconotide use for the severe, refractory chronic pain population (Dewilde, 2009). This article discussed the results of a cost-effectiveness model for IT ziconotide versus "best supportive care," from a UK NHS perspective. The simulation model used three studies from which to base the clinical assumptions for ziconotide (Rauck 2006, Webster 2008 and Wallace 2006, all of which are reviewed independently in this evidence review). The authors report a base case incremental cost-effectiveness ration (ICER) of £27,443 per QALY with a 95% CI between £18,304 and £38,504. A probabilistic sensitivity analysis was performed and the authors concluded that the model was robust to most assumptions, noting the most sensitivity to the dosage of ziconotide and discount rates. The sensitivity analysis showed variability in the ICER due to ziconotide dosing assumption changes, ranging from a low of £15,500 (95% CI £8,206–£25,405) with 0.15mg/hour to a high of £44,700 (95% CI £30,541–62,670) with 0.45mg/hour dosing (from a base case rate of 0.26mg/hr).

This cost-effectiveness model is limited by the reliance on several different sources of data as the basis for assumptions, the lack of long-term data from which to base model assumptions (the authors note a 3-year maximum to reference data), and the use of expert opinion as the basis for some assumptions. The potential for bias therefore, limits the strength of the results.

Does any evidence exist on how to minimise the complications of using Ziconotide including the monitoring and dosing of patients?

There is some evidence to suggest that adverse events can be decreased using lower doses and slower titrations of ziconotide, particularly Dupoiron (2012), Staats (2004), Rauck, (2006), and Alicino (2012). Usual best practices for avoiding complications with IT devices or pumps were not reviewed.

3. Research questions

1. Is ziconotide via intrathecal drug delivery clinically effective in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?

2. Is ziconotide via intrathecal drug delivery cost effective in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?

3. Is ziconotide via intrathecal drug delivery safe to use in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management?

4. Does any evidence exist on how to minimise the complications of using ziconotide including the monitoring and dosing of patients?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of eviden	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
N/A	Systematic	N/A	N/A	Other	N/A	N/A	N/A	N/A	Mercadante, Sebastiano; Porzio, Giampiero; Gebbia, Vittorio. Spinal analgesia for advanced cancer patients: an update. Crit. Rev. Oncol. Hematol. 2012;82(2):227-232.	N/A	N/A	This is a qualitative review of the evidence relating to intrathecal analgesia for advanced cancer patients. Regarding IT ziconotide use, the authors conclude, "some adjuvant drugs such as clonidine, ketamine, betamethasone, meperidine, and ziconotide may be promising agents, but several problems have to be solved before they can be used in the daily practice." The review cites only 4 articles related to ziconotide (Penn 2000, Staats 2004, Wallace 2008, and Ellis 2008), all of which were independently reviewed for this policy development. Therefore, this systematic review was not further evaluated or graded in the evidence review.

1-	Systematic	As per intervention numbers	Combination with morphine, n=25 (Webster, 2008): IT morphine was added to to IT ziconotide during the titration phase; patients could continue with combination therapy or return to ziconotide montherapy during the extension phase. (ziconotide dose: 4.8-24.20 mcg/d) Combination with morphine, n=26 (Wallace, 2008): IT ziconotide was added to IT morphine during the titration phase; patients could continue with combination therapy or continue with ziconotide montherapy during the extension phase. (ziconotide dose: Titration: 0.60–7.20 mcg/d; Extension: 0.84-4.20 mcg/d) Combination with morphine, n=1 (Madaris, 2008): IT ziconotide was added to IT morphine (ziconotide dose: 0.5-4.5 mcg/d) Combination with hydromorphone, n=1 (Saulino, 2007): IT hydromorphone was added to IT ziconotide (ziconotide dose: 2.4-11.0 mcg/d) Combination with baclofen, n=7 (Saulino, 2009): 5 patients had ziconotide added to baclofen therapy; 2 patients had baclofen added to ziconotide therapy (ziconotide dose: 1.2-16.0 mcg/d Multiple IT drug Combination, n=16 (T. Deer, unpublished data, March 2009): IT ziconotide	Other	Combo with morphine, n=25: Efficacy and safety Combo with morphine, n=26: Efficacy and safety Combo with morphine, n=1: Efficacy and safety reported Combo with hydromorphone, n=1: Efficacy and safety reported Combo with baclofen, n=7: Efficacy and safety reported Multiple IT drug combo, n=16: Efficacy and safety reported Multiple IT drug combo, n=37: Efficacy and safety reported Multiple IT drug combo, n=1: Efficacy and safety reported	Combo with morphine, n=25: Mean VASPI scores improved by 26.3% from baseline to the end of the titration period, mean VASPI scores (every 8 weeks) during the extension period varied (range -0.4% to 35.0%). Categorical Pain Relief Scale (CPRS): 68% during titration and 77.8% at the end of the extension period had "moderate" or "a lot" of pain improvement during titration. CGI scores also showed an improvement in pain levels. Systemic opiod use was shown to decrease. Treatment-related side effects noted in over 10% of study participants were: dizziness, peripheral edema, pruritis, nausea. "No serious treatment-emergent AEs that were were considered to be related to the study drugs were reported." Combo with morphine, n=26: Mean VASPI scores improved during the titration period (14.5%) and varied during the extension period (-0.4% to 42.8%). CPRS (56% and 58.8% after titration and extension, respectively) and CGI (68% and 64% after titration and extension, respectively) scores also showed improvement. Related	N/A	NA	Wallace, Mark S.; Rauck, Richard L.; Deer, Timothy. Ziconotide combination intrathecal therapy: rationale and evidence. Clin J Pain 2010;26(7):635-644.	N/A	N/A	This is a qualitative review of the evidence surrounding intrathecal combination therapy with ziconotide. Both clinical and preclinical studies were included in the published review, however, only the clinical data has been included in this summary of the article. 8 clinical studies were noted (including 2 retrospective analyses, 2 open-label trials, 1 case series and 3 case reports). The review concludes that there is some data supporting the use of ziconotide in combination with other IT medications, but that "strong evidence-based data are limited." The authors also note the limited data surrounding safety of ziconotide combination therapy, highlighting that there is a possibility that new or more severe AEs may arise with combination therapy. Overall, the authors felt the combination therapy data was limited and supported a need for "controlled, long-term clinical trials." The review is a well conducted qualitative review, but the small study sizes, lack of statistical analysis and lack of details on many of the study's methods limit the quality of this publication.

			added to regimen (patients were on oral and IT opiod regimens) (ziconotide dose: Start: 0.5 mcg/d; Week 12: 0.6-5.7 mcg/d) Multiple IT drug Combination, n=37 (krakovsky, 2007): IT ziconotide in combination with "other IT drugs" (ziconotide dose: NR) Multiple IT drug Combination, n=1 (Stanton-Hicks, 2006): IT ziconotide added (to IT sufentanil and bupivacaine) (ziconotide dose: 0.5-24.0 mcg/d)			AEs 15% or more were: confusion, dizziness, abnormal gait, hallucinations, and anxiety. Elevated CKs were also reported in 3 patients. Combo with morphine, n=1: Pain score, function and mobility improved, no recurrent granulomas and no AEs experienced. Combo with hydromorphone, n=1: Low pain scores were noted for 15 months; increased need for catheterisation was reported as an AE Combo with baclofen, n=7: VASPI scored improved from baseline at the last evaluation. 1 patient reported nausea and vomiting as an AE (thought related to transdermal fentanyl); 1 patient reported sedation, urinary hesitancy, loss of bladder control and anorexia (all resolved with either decreasing oral baclofen or IT ziconotide). Multiple IT drug combo, n=16: 1 patient had increased pain and depression and ziconotide was discontinued; no other AEs were reported. Of the other 15 patients that had 12-weeks of ziconotide combo therapy, 20% had "substantial pain relief,"						

						66.7% had "no to moderate pain relief," and 13.3% reported "increased pain." Multiple IT drug combo, n=37: Efficacy outcomes reported: 83.8% with improved pain control, 24.3% increased activity, 10.8% decreased IT opiod dose, 13.5% decreased IT adjuvant dose(s) (bupivacaine and clonidine) , and 16.2% decreased oral opiod doses. No AEs were reported. Multiple IT drug combo, n=1: Decreased pain (VAS score) reported, no relevant AEs were reported.						
N/A	Systematic	N/A	Literature searched: various databases for articles, and association meeting abstracts and posters (subject: ziconotide trialing methods)	Other	Systematic review (safety and efficacy of different methods of ziconotide trialing)	N/A	N/A	N/A	Burton, Allen W.; Deer, Timothy R.; Wallace, Mark S.; Rauck, Richard L.; Grigsby, Eric. Considerations and methodology for trialing ziconotide. Pain Physician 2010;13(1):23-33.	This review concluded small sample sizes and lack of controlled trialing limited the evidence, and therefore the relative safety and efficacy of different methods could not be determined (the authors concluded that all 3 mthods were viable options, non more superior based on the current evidence, and called for future controlled trials for more evidence). The authors also noted that it was not possible to determine if trialing was predictive of longer term response.	N/A	The publications included in this review are all either abstracts or posters (not full articles), editorial / expert opinion, or already included elsewhere in this CER. Therefore, this systematic review was not further evaluated or graded in the evidence review.

N/A	Systematic	N/A	Systematic review of the published literature (databases: PubMed, EMBASE, CINAHL) on ziconotide in neuropathic pain	Other	Systematic review (efficacy and safety in neuropathic pain)	N/A	N/A	N/A	Rauck, Richard L.; Wallace, Mark S.; Burton, Allen W.; Kapural, Leonardo; North, James M.. Intrathecal ziconotide for neuropathic pain: a review. Pain Pract 2009;9(5):327-337.	Evidence limitations noted: no direct comparison trials for refractory neuropathic pain. "In this review, the evidence for the use of ziconotide, limited data on the specific subgroup of patients with neuropathic pain (often combined neuropathic and non-neuropathic pain patients), case studies reported raise concern for selection bias. Drug limitations noted: variable therapeutic window, severity of AEs, The authors noted a need for more controlled studies to determine the long-term safety, efficacy and effects on QoL.	Low starting dose and slow titration may improve the safety profile	The clinical publications included in this review are all either abstracts or posters (not full articles), case reports (n=1), or already included elsewhere in this CER. Therefore, this systematic review was not further evaluated or graded in the evidence review.
N/A	Systematic	N/A	Literature search: Databases, Medtronic representative advice on articles to screen, search of "personal files, journals, and books," and bibliography review of screened articles. (subject: effectiveness and complications of IT opioid or ziconotide via programmable pump, not related to spasticity or specific diseases, where either the opioid or ziconotide was the first IT drug)	Other	Systematic review (effectiveness and complications, programmable pump, IT opioid or ziconotide)	6 articles (effectivness and complications); 4 articles (complications only); 0 randomized trials of ziconotide.	N/A	N/A	Turner, Judith A.; Sears, Jeanne M.; Loeser, John D.. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. Clin J Pain 2007;23(2):180-195.	No studies on ziconotide met the inclusion criteria for effectiveness or complications to be included in this review	N/A	No studies on ziconotide met the inclusion criteria of this systematic review. Therefore, this systematic review was not further evaluated or graded in the evidence review.

N/A	Systematic	N/A	Literature review: PubMed/MEDLINE database (1966-June 2006), "data provided by the manufacturer, the FDA medical review, and abstracts from American Pain Society annual meetings (2001–2006)." Note the database search was for randomized, double-bling, placebo-contolled trials only. Subject: The efficacy and safety of ziconotide for chronic pain	Other	Systematic review (efficacy and safety in chronic pain)	No studies of direct comparison of zicontoide versus other IT or systemic analgesics were found	N/A	N/A	Lynch, Shalini S.; Cheng, Christine M.; Yee, Jennie L.. Intrathecal ziconotide for refractory chronic pain. Ann Pharmacother 2006;40(42223):1293-1300.	AEs of note with ziconotide include: neuropsychiatric AEs (including depression, cognitive impairment, and hallucinations), depressed levels of consciousness, elevated CK levels, and meningitis (from possible contamination of the IT device)	The authors state that, "in double-blind, placebo-controlled studies, ziconotide significantly improved patient perception of pain from baseline to the end of the study periods, which ranged from 11 to 21 days. Patients enrolled in clinical trials were intolerant of or refractory to other treatment modalities." They conclude that ziconotide is an option for patients with severe, refractory pain where the potential benefits outweight the risks. They also call for comparative studies to be done going forward.	The clinical publications included in this review are all either abstracts or posters (not full articles), publications not found within a peer-reviewed journal (e.g. "Prialt (ziconotide intrathecal infusion) formulary submission dossier," prescribing information writen by the manufacturer, and "FDA medical review of Prialt") or already included elsewhere in this CER. Therefore, this systematic review was not further evaluated or graded in the evidence review.

1+	RCT	Randomised to ziconotide (n = 112), placebo (n = 108)	Study protocol: Initial screening visit, 3-week weaning (off all IT medications), 1-week stabilisation, 3-week treatment (double-blind, randomised to either IT ziconotide or IT placebo) Dosing note: ziconotide starting dose of 0.1 mg/hour (2.4 mg/day), up titration by time increments of at least 24 hours and dose increments of 0.05-0.10 mg/hour (1.2-2.4 mg/day) until pain relief or intolerance (max dose set at: 0.9 mg/hour (21.6 mg/day)). Downward titration was allowed at anytime. Placebo was given at equivalent infusion rates. No other IT drugs were allowed. Other systemic medications were allowed (including opioids).	Clinical effectiveness of the intervention	Mean percentage change in VASPI score (baseline to Week 3) in the ITT population. Note that treatment responders were pre defined as those with a ≥ 30% improvement in VASPI scores (baseline to Week 3).	Mean change in VASPI scores: 14.7% in the ziconotide-treated group versus 7.2% in the placebo group (P = 0.036)	Secondary efficacy outcomes: mean percent change in VASPI scores (baseline to to week 1 and week 2), CGI Patient Satisfaction scores, CGI Overall Pain Control scores, CPRS scores, and the percentage of treatment responders at termination. Note that the ITT population was used for primary and secondary VASPI score related efficacy outcomes, as well as all safety analyses. "Observed data" was used for the analysis of other efficacy outcomes.	Week 1 efficacy (mean VASPI score improvement): 16.6% (ziconotide), 5.0% (placebo), p = 0.0026. Week 2 efficacy (mean VASPI score improvement): 13.8% (ziconotide), 8.2% (placebo), p=0.12. Treatment responders at week 3 (≥ 30% VASPI score improvement): 16.1% (ziconotide), 12.0% (placebo), p = 0.39. Termination CGI Satisfaction scale ("a lot" or "complete" satisfaction): 28.4% (ziconotide), 12.1% (placebo). Termination CGI Overall Pain Control ("very good" or "excellent"): 11.9% (ziconotide), 0.9% (placebo). Global McGill Pain Relief score: ziconotide verus placebo (p=0.026 in favor of ziconotide). CPRS scores: ziconotide versus placebo (p=0.0596). Week 3 TOPS questionnaire mean for QoL: ziconotide 3.9, placebo 1.8, p = 0.1837. Week 3 opioid use mean decrease: 23.7% (ziconotide), 17.3% (placebo), p=0.44.	Rauck, Richard L.; Wallace, Mark S.; Leong, Michael S.; Minehart, Michael; Webster, Lynn R.; Charapata, Steven G.; Abraham, Jacob E.; Buffington, Daniel E.; Ellis, David; Kartzinel, Ronald; Ziconotide 301 Study Group. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage 2006;31(5):393-406.	Treatment period AEs: 92.9% of patients (ziconotide group) versus 82.4% of patients (placebo group), p = 0.023. AEs of mild or moderate severity: 83.6% (ziconotide) versus 83.8% (placebo). There was a significant difference between ziconotide (more) and placebo (less) for CNS-related AEs: dizziness, confusion, ataxia, abnormal gait, and memory impairment Treatment period SAEs: 11.6%, 13/112, 19 SAEs (ziconotide) versus 9.3%, 10/108, 25 SAEs (placebo), p = 0.57. SAEs related to study drug: 1.8%, 2/112 (ziconotide) versus 1.9%, 2/108 (placebo). "Ziconotide-related SAEs included chest pain, hypertension, ataxia, dizziness, and neuralgia." Discontinuation due to AEs in the treatment period: n = 6, 5.4% (ziconotide) versus n = 5, 4.6% (placebo), p = 0.80. Other discontinuation reasons in the treatment period: n=2 (ziconotide) and n=2 (placebo) for lack of efficacy, n=1 (ziconotide) for voluntary withdrawal of consent, n=1 (placebo) died from VFib.	Low dropout rates: "The improved retention rate in this study is likely a result of the low-dose, slow titration schedule, which allowed for individualization of dose by the physician for each patient." 87% of patients that received ziconotide expressed a desire to continue it in an open-label follow-up study The authors conclude: "Ziconotide, a new nonopioid analgesic, reduced pain as measured by the VASPI in patients with severe chronic pain who were intolerant of and/or refractory to treatment with other analgesics including IT morphine. Using the slow dose titration regimen starting at 0.1 mg/hour (2.4 mg/day) and titrating to a mean dose of 0.29 mg/hour (6.96 mg/day) over three weeks, the degree	This publication reports on the results of a randomised, double-blind, placebo-controlled trial of IT ziconotide. The study design was well-developed with a 3-week "weaning period" (of IT medications), followed by a week long "stabilization period," before the 3-week randomised treatment study protocol began. With 220 patients randomised, the study was well powered (80%, 110 patients, 39.5% standard deviation, 5% level of significance) for a 15% change in the mean VASPI score at week 3 (versus baseline). Patients had chronic, severe, refractory pain that was mostly neuropathic in etiology (mean VASPI score: 80.7, mean duration: 14-15 years, 97% considered refractory, 90% had prior IT morphine). Although the primary end point was reached, the clinical significance of reaching this endpoint is not as clear. The study's primary end point analysis demonstrated a significant (P = 0.036) mean change in VASPI score from baseline with ziconotide treatment (14.7%) versus placebo (7.2%) at 3 weeks. However, the authors had pre-determined the definition of "responders" as a 30% change in VASPI score from baseline, and the mean VASPI change from baseline in the ziconotide group was only 14.7%. Additionally, although the primary endpoint (for which the study was powered) was the 3-week data, the 1-week and 2-week data were also analysed as secondary endpoints. As with the 3-week data, the 1-week mean change in VASPI score in the ziconotide group was significantly different from the placebo group with a greater than 95% confidence (p=0.0026). However, the 2-week data point revealed a difference between the ziconotide (13.8% mean VASPI score) and placebo (8.2% mean VASPI score) groups that did not reach the set 95% confidence level for significant difference, though the p-value was still quite low at p=0.1211. Additional positive study results showed significant improvements in the CGI Satisfaction (28.4% Z vs 12.1% Pl, p=0.0027) and CGI Overall Pain Control scales (11.9% Z vs 0.9% Pl, p=0.0004), Global McGill Pain Relief scores (p=0.026), and the BPI "enjoyment of life subscale" (42.2% Z vs 27.4% Pl, p=0.019). Unfortunately, results also revealed no

									Termination BPI enjoyment of life subscale (≥1 unit improvement): 42.2% (ziconotide), 27.4% (placebo), p=0.019. No difference in BPI subscales for: sleep, relations, work, mood, and walking		Other safety outcomes (baseline to termination): - Vital signs: "no clinically significant changes" - ECG: "no clinically significant changes" - Uric acid, LDH, CK: "statistically significant shifts from normal at baseline to above normal at termination" for ziconotide group (1 had unrelated hypokalemia, and 4 had muscular sysmptoms)	of pain relief was less than that noted in the two previous controlled trials of ziconotide, but better patient retention and an improved safety profile were observed. Taken together, the three controlled trials demonstrate that, to achieve the best overall treatment outcome, slow titration of ziconotide at low doses is necessary to identify each patient's individualized therapeutic window. As the most comprehensively studied IT analgesic in controlled trials, ziconotide appears to have a place in the management of severe chronic pain." Note that the 2nd of the previous studies they refer to includes a referece to "data on file" from Elan Pharmaceuticals.	statistically significant difference in CPRS scores, mean TOPS scores (3.9 Z vs 1.8 Pl, p=0.1837), other BPI subscales (sleep, relations, work, mood and walking), and the mean decrease in opiod use (23.7% Z vs 17.3% Pl, p=0.44). The authors note that this trial was set to a slower titration and lower maximum dose of IT ziconotide than previous studies in response to the high adverse event rate in earlier trials of IT ziconotide. The prior studies referenced are Staats 2004, which is included in this CER separately, and Mather 2002 / Elan Pharmaceuticals "data on file" which was not independently reviewed for this CER as the Mather aritcle is a nonsystematic review and the Elan data was "data on file" (not published data). During the treatment phase of the study, there was a significantly higher rate of AEs in the ziconotide group (92.9% Z vs 82.4% Pl, p=0.023), however most AEs were mild or moderate (83.6% Z, 83.8% Pl). There was no significant difference in the SAEs reported during the treatment phase (11.6%, 19 SAEs Z vs 9.3%, 25 SAEs Pl, p=0.57), and only 1.8% (2/112) of patients in the ziconotide group had a treatment-related SAE (vs 1.9%, 2/108, in the placebo group). The study demonstrated, "ziconotide-related SAEs included chest pain, hypertension, ataxia, dizziness, and neuralgia." In conclusion, although the primary endpoint (mean change in VASPI scores versus placebo) was met, the 14.7% mean improvement in VASPI scores reported did not reach the 30% threshold set for defining "responders" to treatment (understanding that the 30% threshold definition is for individuals, not a group mean, this is still noteworthy). Additionally, not all secondary endpoints were met in this study. The authors conclude that their slower titration (with a low maximum dose) resulted in a better safety profile than the previous studies. Given results of the other studies were not available for review in one instance (i.e. no formal indirect comparison is made), and of a different study designs and populations (reviewed separately in this CER), the accuracy of this comparative statement is uncertain. However, 92.9% of those in the ziconotide group did experience an AE (significantly higher than the 82.4% in the placebo group), though most (83.6%) of these were mild or moderate in severity. The SAE rate was not different (Z vs Pl) and chest pain, hypertension, ataxia, dizziness, and neuralgia were reported as ziconotide-related SAEs.

3	Case series	8 patients	IT ziconotide was added to IT morphine plus bupivacaine in 8 patients with chronic, refractory (VAS pain score ≥5, despite 3 successive 20% dose increases of IT morphine) cancer pain. Ziconotide dosing: Starting dose 0.5-1.0 µg/day, mean increases 0.5 µg every 4-7 days if required, maximum dose 10 µg/day, mean dose 4.9 µg/day.	Clinical effectiveness of the intervention	N/A	N/A	N/A	N/A	de la Calle Gil, Ana Bella; Peña Vergara, Isaac; Cormane Bornacelly, María Auxiliadora; Pajuelo Gallego, Antonio. Intrathecal Ziconotide and Morphine for Pain Relief: A Case Series of Eight Patients with Refractory Cancer Pain, Including Five Cases of Neuropathic Pain. Neurol Ther 2015;0(0):0.	Pain intensity was reduced in all patients after 3-5 days.	Of the eight patients, three died for reasons unrelated to ziconotide, three discontinued treatment due to adverse effects (predominantly psychoneurological disorders), and one patient is still receiving treatment. One patient discontinued ziconotide due to confusion and delirium. Due to continued lack of pain control with intrathecal morphine, intrathecal fentanyl was initiated; however, effective pain relief was not achieved with 1500 µg/day. Ziconotide was restarted and the patient then achieved pain control.	According to the abstract reviewed, this is a publication documenting 8 case reports of patients with chronic, uncontrolled cancer pain (5 of 8 confirmed as neuropathic pain) treated with combination IT ziconotide and IT morphine plus bupivacaine. The abstract reports that "pain intensity was reduced in all patients after 3-5 days." Only 1 of the 8 patients was reported as being maintained on IT ziconotide at the end of the reporting period and 3 of the 8 patients discontinued IT ziconotide due to AEs. The authors conclude, "On the basis of our clinical experience, we recommend adding ziconotide to intrathecal opioid-based therapy in cancer patients with neuropathic pain inadequately controlled by intrathecal morphine alone." This report represented very low level evidence as a case series and with a low number of patients (n=8). In addition, there was a high discontinuation rate (3 or 8) due to AEs noted. Therefore, the author's conclusion that this evidence supports any recommendation is not likely to be endorsed in this CER. The full article was not reviewed.

2-	Cohort	23 patients	Up to 3 ziconotide bolus injections (first dose = 2.5 µg) per "a comprehensive expert-based, agreed-upon algorithm." Evaluation via the algorithm was based on analgesic effects and AEs experienced.	Clinical effectiveness of the intervention	Change in VASPI score. Note that treatment responders: PPR ≥ 30% and no significant AE on 2 consecutive administraions at the same dose.	Results: - 2/23 (13%) were responders per the algorithm criteria (however, 7/23 or 30% achieved ≥ 30% pain reduction on a least one injection - 17/23 (74%) were non-responders - 3/23 (13%) did not complete the algorithm Statistical analysis: - pre-injection VASPI-now verses hourly for six hours after injection were different (p = 0.047, mean ziconotide dose of 2.75 µg, only the pre-injection differed from any other time point result) - The VASPI-mean versus pre-injection VASPI-now (p = 0.019, mean was lower) - Pre-injection VASPI-24h versus post-injection VASPI-24h (p = 0.078, not different) - The PGIC mode after 6 and 24 hours (not different)	N/A	N/A	Bäckryd, Emmanuel; Sörensen, Jan; Gerdle, Björn. Ziconotide Trialing by Intrathecal Bolus Injections: An Open-Label Non-Randomized Clinical Trial in Postoperative/Posttraumatic Neuropathic Pain Patients Refractory to Conventional Treatment. Neuromodulation 2015;18(5):404-413.	Safety outcomes reported: - AEs: 15/23 patients had 33 AEs (24 were probably related to ziconotide, 7 were possibly related; 17 mild, 16 moderate) on 18 occasions. The most common AEs were: dizziness, tiredness, headache, nausea / vomiting, and itch. "All AEs were consistent with the SPC, and all resolved." - SAEs: None reported - CK levels: 3.52 ± 0.77 µkat/l before injection versus 3.15 ± 0.70 µkat/l one week after (p = 0.286, N = 11) - MAP and HR over time were different (p < 0.001 for both measurements), but there were no clinical CV effects CV effects noted.	As per the primary endpoint outcomes: Only 13% of study participants were responders by the study algorithm definition, but 30% had at least a 30% improvement in pain with at least one ziconotide injection. The authors report a NNT of ~3 for clinically significant pain relief based on this second figure.	This article reports on a small trial (n=23)of ziconotide bolus therapy for chronic pain. VASPI scores were reported by patients at set intervals for efficacy analysis. Results of the study reported that 13% did not complete the algorithm after the first injection, 74% were classified as "non-responders," and 13% responded per the algorithm criteria Despite this low overall "response" rate (13%), 30% of patients did achieve a response to at least one injection (≥ 30% pain reduction). Analysis of the results showed significant changes (p=0.047) in VASPI scores reported before and after injection (hourly for 6 hours, mean ziconotide dose of 2.75µg). The mean post-injection VASPI score (hourly x 6 hours) was lower than the pre-injection score (p=0.019), but the 24-hour post-injection score did not quite reach statistical significance for being different from the 24-hour pre-injection score (p=0.078). There were 33 AEs over 18 events in 15 patients (17 mild, 16 moderate; 24 probably ziconotide-related; 7 possibly related). There were no SAEs. The most common AEs were dizziness, tiredness, headache, nausea / vomiting, and itch. Additionally, there were changes in MAP and heart rate (p<0.001 for both), but these were not clinically significant. The authors concluded that: "1) ziconotide bolus injection trialing seems feasible; 2) the proportion of responders in the present study was low, but there was a subgroup of responders; 3) AEs were as expected according to the SPC, and no SAE occurred; 4) the predictive power of ziconotide bolus trialing remains unclear; 5) the pharmacological profile of ziconotide (with very slow tissue penetration due to high hydrophilicity) calls the rationale for bolus trialing into question; 6) patients refractory to all available treatment modalities are a reminder of the need for more research into the mechanisms of different pain conditions." The evidence found in this study supports this conclusion, although the small study size, open-label methodology, and multiple secondary / other endpoint analyses limit the strength of this study's design and results.

3	Case series	16 patients	Inital dual bolusing trial, followed by device implantation, then ziconotide was started with a flex dosing strategy, weighted during nocturnal dosing. The initial ziconotide dose was dependent on the trial dose, and use nocturnal flex dosing, the dose was titrated for therapeutic effect (every 7 days by 0.1 microgram increments).	Safety of the intervention	Tolerability of ziconotide at three months	The authors report that all enrolled patients met the endpoint	Outcomes reported: change in VAS, AEs, durability of therapy, and change in systemic opioid use	Sustainability for ≥ 3 months: 100% 4 months: 75% were maintained on ziconotide monotherapy 6 months: 70% were maintained on ziconotide monotherapy Average decrease in NRS: from 9.06 to 1.8 Average opioid reduction: 91.5% Most common AEs leading to discontinuation: urinary retention and visual hallucinations. SAEs: None Complications: None	Pope, Jason E.; Deer, Timothy R.. Intrathecal Pharmacology Update: Novel Dosing Strategy for Intrathecal Monotherapy Ziconotide on Efficacy and Sustainability. Neuromodulation 2015;18(5):414-420.	No complications or SAE reported. The authors report that all side effects were self-limited and resolved within 96 hours of stopping ziconotide.	The authors conclude that there may be tolerability improvements with flex dosing and advise further (randomised, prospective, well-powered) studies to "critically evaluate" the findings in this case series.	This is a case series of 16 patients given IT ziconotide with a continuous infusion "flex dosing" strategy. 100% of the 16 patients were tolerating the study drug at 3 months (with 75% at 4 months, and 70% at 6 months). The average numerical rating scores decreased from 9.06 to 1.8 (no statistical analysis of the significance). AEs leading to discontinuation were most commonly urinary retention and hallucinations. There were no SAEs. This is a small observational case series, limiting the ability to draw conclusions of any significant strength from the findings. The authors conclude that there may be tolerability improvements with flex dosing and advise that "further randomized, prospective, higher-powered studies are needed to critically evaluate the conclusions suggested by this limited prospective case series."
3	Case series	15 patients	After initial bolus trial success, patients moved to the continuous treatment phase. IT ziconotide: starting / minimum daily infusion 1.1 ± 0.1 mcg/day, 4-12 week titration (max 20% increase every 3-4 weeks, concomittant IT bupivacaine and / or opioid dosing maintained or decreased, oral medications not changed)	Clinical effectiveness of the intervention	IT medications / doses, oral medications / doses, pain intensity, AEs, ziconotide discontinuation reason (time points: 3, 6, 12, 18, and 24 months)	- 15 patients enrolled, 4 failed the initial bolus trial (3 had AEs, all 4 did not have pain releif), 11 entered the continuous treatment phase. - AEs: 7/11 had AEs resulting in discontinuation (2 of these had improvement in pain) - Sustainability: 36% (4/11) continued for 24 months (at 24 months, mean dose 7.6 ± 3.7 mcg/day, median dose 8.2 mcg/day); mean time to discontinuation secondary to AEs: 7.4months (median 8 months) - Tolerated dose of ziconotide: mean 7.6 ± 3.7 mcg/day, median 8.2 mcg/day (range: 3 and 12 mcg /day) - Pain control: Mean (± SEM) change from baseline in pain control scores (8.1 ± 0.7, n = 11) was: 6.3 ± 0.3 (n = 9) at 3 months (p < 0.02), 6.8	N/A	N/A	Hayek, Salim M.; Hanes, Michael C.; Wang, Connie; Veizi, I. Elias. Ziconotide Combination Intrathecal Therapy for Noncancer Pain Is Limited Secondary to Delayed Adverse Effects: A Case Series With a 24-Month Follow-Up. Neuromodulation 2015;18(5):397-403.	Initial bolus trial AEs in 3 patients (at a mean bolus dose of 3.5 mcg): presyncope, nausea / GI upset, dyspnea, and lower extremity numbness Continuous treatment AEs: confusion/altered mental status (n = 6; 55.5%), presyncope (n = 4; 36.4%), memory loss (n = 3; 27.3%), nausea/GI upset (n = 2; 18%), and syncope (n = 1; 9%). Continuous treatment discontinuation data: CNS-related AEs in all 7 patients, mean dose at discontinuation secondary to AEs was 4.79 ± 1.96 mcg/day (median: 2.69 mcg/day; range: 1.13–13.6 mcg/day)	N/A	This is a retrospective review of a study where patients were trialled on and, in those with a successful trial, subsequently monitored on continuous IT ziconotide therapy for c. two years. The study is limited by the small number of patients (n=16) and nonrandomised, retrospective observational design. The study showed "changes in NRS scores from baseline were only statistically significant at three months (N = 9, p < 0.02) after initiation of ziconotide and there was a trend for loss of effectiveness coinciding also with a discontinuation of treatment due to AEs upon increased doses ." The authors conclude that "combination IT therapy with ziconotide, hydromorphone or fentanyl, and bupivacaine appears to be effective in only a small group of patients with refractory chronic noncancer related pain. Our low success rate was primarily attributed to the high rate of AEs experienced by patients. Furthermore, patients who were stable on ziconotide treatment did not appear to have sustained improved analgesia in the long term (at least two years as described in this study)." This study provides low level evidence in support of the authors' conclusions.

						± 0.9 (n = 9) at 6 months, 8.0 ± 0.7 (n = 6) at 12 months, 6.3 ± 0.8 (n = 5) at 18 months, and 8.5 ± 0.6 (n = 4) at 24 months (only the 3 month change was statistically significant, and "there was a trend for loss of effectiveness coinciding also with a discontinuation of treatment due to AEs upon increased doses") - Oral opioid use: 6 of the 7/11 patients on oral opioids were weaned off (oral dose was low at < 40mg morphine eq/day)						
3	Case report	1 patients	Bolus dose of IT ziconotide (dose not reported in abstract)	Safety of the intervention	N/A	N/A	N/A	N/A	Horazeck, Christian; Huh, Albert S.; Huh, Billy K.. Acute rhabdomyolysis in a patient with long-term exposure to intrathecal ziconotide: a case report. Pain Pract 2015;15(3):E34-39.	Acute rhabdo with IT ziconotide bolus	N/A	This is a single case report of a patient who had acute rhabdomyolysis after an IT bolus dose of ziconotide. The patient had previously been treated with IT ziconotide for 2 years, and this was stopped due to "moderate side effects resulting from dose escalation." The patients was hospitalised and treated for acute rhabdomyolysis with resolution of symptoms. This single case report only offers very low level evidence, but the possibility of developing rhabdomyolysis with IT ziconotide is noted. The full article was not reviewed.
3	Case report	1 patients	Continuous IT zicontoide (rate: 4.9mcg/24hours)	Safety of the intervention	N/A	N/A	N/A	N/A	Phan, Stephanie V.; Waldfogel, Julie M.. Ziconotide-induced psychosis: a case report. Gen Hosp Psychiatry 2015;37(1):97.e11-12.	Psychosis	N/A	This is a single case report of a patient with 3 weeks of auditory hallucinations and paranoid ideation after being started on IT ziconotide 3 months prior (rate was 4.9 mcg/24 hours on admission). Psychotic symptoms resolved with discontinuation of ziconotide and 10 days of risperdol treatment. The single case report and inability to prove a cause-effect relationship limits this report. This is, therefore, very low level evidence, but it highlights a possible psychiatric side effect of IT zicontoide. The full article was not reviewed.

3	Case report	1 patients	IT Ziconotide (rate: 1ug/day)	Clinical effectiveness of the intervention	N/A	N/A	N/A	N/A	Narain, Sachin; Al-Khoury, Lama; Chang, Eric. Resolution of chronic migraine headaches with intrathecal ziconotide: a case report. J Pain Res 2015;8(0):603-606.	N/A	Resolution of neuropathic pain as well as chronic migraines over an 8 month follow-up	This is a case report of a patient with MS spasticity and neuropathic pain, as well as chronic migraine headaches who had been treated with multiple prior therapies with some improvement, but not complete relief of migraines. IT Ziconotide was added for neuropathic pain and resulted in resolution of her migraine headaches as well as the neuropathic pain in 8 months of follow-up. This is a single case report which provides very low evidence, and no proof of casual relationship, but resolution of chronic migraines was noted in this patient on low-dose IT ziconotide. The full article was not reviewed.
3	Case report	1 patients	IT ziconotide added to the patient's IT baclofen (dose not reported in abstract)	Clinical effectiveness of the intervention	N/A	N/A	N/A	N/A	Lanzillo, B.; Loreto, V.; Calabrese, C.; Estraneo, A.; Moretta, P.; Trojano, L.. Does pain relief influence recovery of consciousness? a case report of a patients treated with ziconotide. Eur J Phys Rehabil Med 2014;0(0):0.	N/A	Improved consciousness	This is a case report of a patient with unresponsive wakefulness syndrome after traumatic brain injury, who showed marked improvement in consciousness with the addition of ziconotide to IT baclofen. This is a single case report and therefore of very low evidence strength and a causal relationship cannot be proven, however the case of improved consciousness is noted. The full article was not reviewed.

3	Case report	1 patients	IT ziconotide added to the patient's IT baclofen (dose not reported in abstract)	Safety of the intervention	N/A	N/A	N/A	N/A	Pozzi, Marco; Piccinini, Luigi; Giordano, Flavio; Carnovale, Carla; Perrone, Valentina; Pellegrino, Paolo; Antoniazzi, Stefania; Turconi, Anna Carla; Radice, Sonia; Clementi, Emilio. Dyskinesia caused by ziconotide-baclofen combination in an adolescent affected by cerebral palsy. Reg Anesth Pain Med 2014;39(2):172-173.	Dyskinesia	N/A	This is a single case report and therefore of very low evidence strength, of ziconotide-induced dyskinesia of the head / upper limbs. The dyskinesia was noted 2 days after ziconotide had been added to baclofen and it resolved with discontinuation of the ziconotide. The full article was not reviewed.

2-	Cohort	20 patients	Initial bolus dose of 2.5 mcg IT ziconotide; subsequent doses were 2.5 mcg, 1.2 mcg, or 3.75 mcg per protocol (modified per prior response). A good response was defined as at least a 30% improvement from baseline pain VAS without AE on 2 occasions.	Clinical effectiveness of the intervention	Change in pain VAS score	- Mean reduction of pain VAS (overall): 17mm (95% CI, 10 to 23 mm) or about 25% - Mean decrease in VAS (11 responders): 28mm (95% CI, 22 to 34 mm) or 43% - Mean decrease in VAS (nonresponders): 3mm(95% CI, -1 to 7 mm) or 4%	N/A	N/A	Mohammed, Salma I.; Eldabe, Sam; Simpson, Karen H.; Brookes, Morag; Madzinga, Grace; Gulve, Ashish; Baranidharan, Ganesan; Radford, Helen; Crowther, Tracey; Buchser, Eric; Perruchoud, Christophe; Batterham, Alan Mark. Bolus intrathecal injection of ziconotide (Prialt®) to evaluate the option of continuous administration via an implanted intrathecal drug delivery (ITDD) system: a pilot study. Neuromodulation 2013;16(6):576-581; discussion 582.	AEs: 76 AEs (14 unrelated to study drug, 3 serious AEs, none required action, elev CK noted) SAEs: 3 in 3 patients (dizziness after 2.5 mcg; double vision, depression, anxiousness, nausea, dizziness, and unsteadiness after 2.5 mcg; and unrelated infected foot)	Treatment efficacy did not vary with sex, center, age, or pain etiology. The authors reported the NNT for benefit was 2.	This is a small cohort study of IT ziconotide bolus injection therapy for chronic pain. The results showed a mean decrease in VAS pain score from baseline of about 25% overall, and 43% in the responder group. A "good" response was defined as at least a 30% change in pain score from baseline with no side effects on 2 occasions. There were 76 AEs, most of which were related to the study drug, but none required intervention. There were 3 SAEs, 2 of which were related to ziconotide. The study is limited mainly by the small number (n=20), lack of blinding, and lack of control group. Overall, this study presents weak evidence. The authors conclude that further (randomised, blinded, large / highly powered) studies, "are needed to determine if bolus dosing with ziconotide is a good predictor of response to continuous IT ziconotide via an intrathecal drug delivery system."

3	Case series	5 patients	Combined spinal-epidural technique (ziconotide vs morphine or hydromorphone) (dose not reported in abstract)	Clinical effectiveness of the intervention compared to existing interventions	N/A	N/A	N/A	N/A	Gulati, Amitabh; Loh, Jeffrey; Puttanniah, Vinay; Malhotra, Vivek. The use of combined spinal-epidural technique to compare intrathecal ziconotide and epidural opioids for trialing intrathecal drug delivery. Pain Manag 2013;3(2):123-128.	N/A	N/A	This is a 5-patient case series of a combined spinal-epidural technique used to compare IT ziconotide and morphine or hydromorphone for chronic pain. The abstract concludes that the "results were used to develop a paradigm to describe how ziconotide can be used in practice." This 5-patient case series inherently only provides very low level evidence. The full article was not reviewed.

2-	Cohort	77 patients	Morphine, clonidine, and ropivacaine were given in combination with ziconotide. Dosing note: target starting dose 1 µg/day, titration increments of 0.25 to 0.5 µg/d every 7 days (minimum of 48 hours), no maximum dose (increased until analgesia)	Safety of the intervention	Incidence of ziconotide-related AEs (with slow titration, low starting dose)	AEs: 44 patients (57%), most common: nausea (23 patients, 30%) as single AE, but neurological complications for overall AEs. AEs requiring discontinuation: 7 patients (9%, 4 (5%) were serious), 5 (all 4 of the serious AEs: depressoin, confusion, visual disorder) were "highly likely" related to ziconotide, all AEs resolved after discontinuation	Efficacy (with slow dosage titration)	- Pain intensity score (numerical scale): Significantly decreased versus baseline at 15, 30, 60, and 90 days, maximum drop after 30 days (8.07 ± 1.27 to 4.14 ± 1.37, p <0.01); mean decrease at one month of 48% (after 2 months, 4.29 ± 2.30, and after 3 months, 4.12 ± 2.07 (p < 0.01) - Mean duration of IT pain analgesia 113.4 (±117.4) days per patient; 6,021 total treatment days (all patients)	Dupoiron, Denis; Bore, Francois; Lefebvre-Kuntz, Daniele; Brenet, Olivier; Debourmont, Sabine; Dixmerias, Florence; Buisset, Nadia; Lebrec, Nathalie; Monnin, Dominique. Ziconotide adverse events in patients with cancer pain: a multicenter observational study of a slow titration, multidrug protocol. Pain Physician 2012;15(5):395-403.	N/A	The authors conclude: SAE rate was lower than in earlier studies, moderate AEs were observed at a similar rate, improved safety profile of ziconotide with low dose initiation (0.5 to 1 µg/d) and slow titration (0.5 µg/d 1-2 times per week), further combo drug studies are needed	This is a non-randomised, observational study of 77 patients assessing the safety of combined IT ziconotide, morphine, ropivacaine, and clonidine in patients with chronic cancer pain. There are two major limitations to this study: the non-randomised observational study design, the use of 4 study medications together limits the ability to determine a causal effect between outcomes and any one of the 4 new medications. Additionally, the patients had various forms of cancer (though a notable 19.5% had pancreatic cancer), and the percentage of patients with neuropathic versus other forms of pain was not reported. The authors used a low starting dose and a slow titration rate for ziconotide in order to try to prevent adverse reactions. 57% of patients reported AEs and 9% of patients had to stop the study drug due to AEs (5% were serious). 30% of patients experienced nausea, but on a combined basis neurologic complications were the most common. The authors noted that "A causal relationship with ziconotide was highly likely for 5 of the 7 patients who experienced adverse events, including all 4 who had serious adverse events (depressive syndrome, confusion)." They also noted that "all adverse events disappeared 2 days after treatment discontinuation." The authors state that the rates of mild - moderate AEs were consistent with other studies, and that the rate of SAEs was lower than in other studies. They conclude that the slower titration of ziconotide is responsible for the seemingly improved side effect profile in this study, however given the possible confounding of 4 other IT medications in this study, the results are not likely to be generalisable. Additionally, there is uncertainty in comparing outcomes across studies with different designs and methodologies. The study results showed a significant improvement in pain intensity (numerical scale) from baseline after 15, 30, 60, and 90 days of IT therapy. The authors also conclude that the "study confirms the efficacy of intrathecal analgesia with ziconotide for relieving refractory cancer pain. These results indicate that multimodal intrathecal analgesia in patients with cancer pain should

												include ziconotide from the outset in order to provide time for subsequent slow titration." However, the study does not definitively provide cause-effect evidence for ziconotide outcomes given the concomittant dosing of 4 other new IT medications, nor is there any evidence reported regarding use of ziconotide in first line presented in the publication. Overall, this study provides weak evidence regarding the efficacy and safety of ziconotide use in combination with other IT therapies. It does not address IT ziconotide as monotherapy.
2-	Cohort	20 patients	IT combination: Ziconotide (starting dose 2.4 ug/day, increased by 1.2 ug/day intervals every 7+ days) and morphine (starting dose calculated based on oral dose) calculated based on its oral daily dose (at an oral/IT ratio of 400/1); doses were titrated for pain control and AEs	Clinical effectiveness of the interventio n	Reduction in VASPI score at days 2, 7, and 28	Percentage changes in VASPI mean scores from baseline: 39 ± 13% (95% CI = 13.61–64.49, p < 0.001) at day 2, 51 ± 12% (95% CI = 27.56–74.56, p < 0.001) at day 7, and 62 ± 13% (95% CI = 36.03–87.89%, p < 0.001) at day 28 (with mean VASPI score of 34 ± 13).	AE rate	Mild AEs observed in 4 patients	Alicino, Ilaria; Giglio, Mariateresa; Manca, Fabio; Bruno, Francesco; Puntillo, Filomena. Intrathecal combination of ziconotide and morphine for refractory cancer pain: a rapidly acting and effective choice. Pain 2012;153(1): 245-249.	N/A	The authors conluded that "an IT combination of low doses of ziconotide and morphine allows safe and rapid control of oral opioid–refractory malignant pain."	This is a small study of 20 patients with non-neuropathic cancer pain refractory to oral opiate use. Study participants were started on IT ziconotide and morphine and changes in VASPI score were noted over a 1 month period. Significant improvements in VASPI from baseline were noted and only mild AEs in 4 patients were related to the study drugs. dditionally, at 28 days, the 95% CI for VASPI improvement did not fall below 30% (a typically used cut off for defining a good response in other studies). The authors conclude that their "study results suggest that an IT combination of ziconotide and morphine, at low doses, allows safe and rapid control of oral opioid–refractory malignant pain. The decrease in VASPI score was significant as early as 2 days after the combination therapy was initiated, and persisted during the 28 days of the study. Mild AEs were observed in a few patients." They call for further, larger studies going forward. The main limitations of this study are the small size, lack of comparator control arm, and the dual study drug design which makes it difficult to assign results to any one of the two interventions.

3	Case series	18 patients	Patients on IT ziconotide were investigated using the Mini International Neuropsychiatric Interview for psychiatric disorders (note mean dose of ziconotide: 4.01 mg/day (+/- 2.37) at 6 months and 5.28 mg/day (+/- 4.12) at one year)	Safety of the intervention	N/A	N/A	N/A	N/A	Poli, Paolo; Ciaramella, Antonella. Psychiatric predisposition to autonomic and abnormal perception side-effects of ziconotide: a case series study. Neuromodulation 2011;14(3):219-224; discussion 224.	See next cell	A good outcome was predefined as a decrease in VAS score of 50% at 6 months or 1 year. Good outcomes observed: 8/18 at 6 months, 10/14 at 1 year (71.42%). 5 AEs: dysesthesia / sensorial hallucination, dry mouth, heartburn, ataxia, and auditory hallucination. 4 patients discontinued after 6 months. 12/18 had a psychiatric comorbidity; panic disorder patients had the most AEs; the 6 patients "without psychiatric comorbidity showed a better outcome without autonomic side-effects" (at 6 months: z-value = 2.19; p = 0.02 with mean rank of 13.50 vs. 6.50; at 1 year no difference seen); "patients without psychiatric comorbidity did not need a lower dose of ziconotide compared with patients with psychiatric comorbidity (mean dose: 3.40 vs. 4.58 mg/day with a z-value of 0.65 at 6 and 2.40 vs. 5.53 mg/day with a z-value of 0.42 at 12 months respectively)."	This is a case series of 18 patients with IT ziconotide therapy. The authors found that all patients with panic disorder had more side effects with ziconotide use, and that the patients without a psychiatric comorbidity had better results with ziconotide (at 6months, change in VAS score was significantly better but not at one year; they were reported to be "without autonomic side-effects", as well). They conclude that "a psychiatric disorder with cholinergic-noradrenergic system impairment could increase some side-effects of treatment with N-type calcium channel blockers." They highlight the importance of treatment of psychiatric disorders in chronic pain patients, especially the need for treatment of panic disorder for patients being considered for ziconotide treatment. This small case series provides weak evidence, limited majorly by the study design.

3	Case series	10 patients	Detox regimen: Days 1-3: IT saline, IV morphine, oral clonidine, ketoprofen, and lorazepam; then slow-release tramadol, oral clonidine, and ketoprofen for 10 days Ziconotide started at end of detox treatment (dosing schedule not reported in abstract)	Other	Efficacy and safety of this rapid detox regimen (withdrawal via the observer-rated opioid withdrawal scale (OOWS), pain intensity via the visual analogue scale, AEs observed)	Withdrawal symptoms: 3 patients (30%), average OOWS decreased from 4.3 +/- 2.5 at day 3 to 1.7 +/- 0.6 at 14 of protocol ($p < 0.05$), average time to resolution of withdrawal symptoms was 4 days (no need for additional medications) Pain intensity: no increase	N/A	N/A	Raffaeli, William; Righetti, Donatella; Sarti, Donatella; Balestri, Marco; Ferioli, Isabella; Monterubbianesi, Maria Cristina; Caminiti, Alessandro. Ziconotide: A rapid detoxification protocol for the conversion from intrathecal morphine--the Raffaeli Detoxification Model. J Opioid Manag 2011;7(1):21-26.	N/A	The authors concluded that the study's "detoxification protocol was effective in preventing withdrawal signs without increasing pain severity, allowing to rapidly convert IT morphine to ziconotide monotherapy in patients who are refractory to morphine."	This is a 10 patient prospective, open-label case series assessing a rapid detox protocol and transition to IT ziconotide, in patients with chronic, refractory (noncancer) pain. The authors state that 30% of patients reported opiod withdrawal symptoms, but these symptoms imporved between day 3 and day 14 of the study (without increasing pain intensity). The full article was not reviewed.
3	Case report	2 patients	Report of 2 patients with suicidality while on ziconotide Note on dosing: "One patient performed suicide under low-dose (cumulative dosage: 779µg) 4 weeks after the onset of intrathecal ziconotide treatment despite sufficient pain relief. Another female patient with a history of depression, but free of symptoms under antidepressive medication since more than 15 years, developed severe suicidal ideation 2 months after ziconotide treatment (cumulative dosage: about 2900µg) with rapid recovery after drug discontinuation."	Safety of the intervention	N/A	N/A	N/A	N/A	Maier, Christoph; Gockel, Hans-Helmut; Gruhn, Kai; Krumova, Elena K.; Edel, Marc-Andreas. Increased risk of suicide under intrathecal ziconotide treatment? - a warning. Pain 2011;152(1): 235-237.	2 patients with suicidality reported	N/A	This is a care report of 2 patients with suicidality while on IT ziconotide. One patient was noted to have a history of depression but had been free of symptoms for more than 15 years, the other patient had raised concern for depression in the past without having been given a diagnosis. The authors conclude in the abstract that these cases "substantiate the suspicion of a causal relationship between ziconotide and suicidality even in symptom-free patients with a history of depression. Therefore, a comprehensive psychiatric evaluation is unavoidable before and during ziconotide treatment." This is very low level evidence. The full article was not reviewed.

2-	Cohort	104 patients	IT ziconotide (Mean initial ziconotide dose was 1.41 ± 0.61 µg/d)	Clinical effectiveness of the intervention	Efficacy (VASPI scores; change from baseline)	- 55/104 patients had ziconotide as first IT drug choice - 72/104 (69%) had ≥ 30% pain reduction (mean dose 4.36 µg/d, within a mean treatment period of 53 days (n=68)) - 45/104 had a > 6 months sustained response (p<0.001), "without treatment interruptions and with relatively stable doses." - 56 patients (53.84%) had a 50% pain reduction (mean treatment period of 82 days (n=52)) - Cancer patients: 20%-50% pain reduction within one month of treatment on average (range: 29-37 days) - Non-cancer patients: 20%-50% pain reduction within 3 months of treatment on average (range: 62-112) - 51% had neuropathic pain	Safety (number and intensity of AEs)	- SAEs: None - AEs (ziconotide related): 66 patients (63.46%), most common: psychomotor disorders (34.61% of patients) manifested as confusion and memory impairment, and asthenia (22.11% of patients). - Most common treatment inturruption reasons: 18.26% AEs (19 non-cancer patients), 6.73% lack of efficacy (6 non-cancer, 1 cancer), 5.76% compliance (5 non-cancer, 1 cancer), 3.84% infusion system-related AEs (4 non-cancer), disease-related death (18 cancer patients and 1 non-cancer patient) - AEs did not always cause discontinuation (18%)	Raffaeli, William; Sarti, Donatella; Demartini, Laura; Sotgiu, Alberto; Bonezzi, Cesare; Italian Ziconotide Group. Italian registry on long-term intrathecal ziconotide treatment. Pain Physician 2011;14(1):15-24.	Limitations noted: retrospective data collection, different methods across different centers (treatment and data collection), no placebo group, some data were missing	The authors concluded that "ziconotide can be used as a first choice for intrathecal pain treatment or in substitution to classic IT drugs (morphine), with good levels of efficacy and long-term safety. Ziconotide did not cause severe side effects. Long-term treatment was attained at stable doses with constant pain relief, without long-term adverse events that caused therapy interruption. This suggests that, once the early side effects were overcome, the responsive patients were not exposed to long-term risks. The constant ziconotide dosages also suggest the absence of tolerance effect."	This is a retrospective cohort study of 104 patients enrolled in an Italian registry for IT ziconotide use. 51% had neuropathic pain. 53% of patients were given ziconotide as their first-line IT therapy. The results showed a ≥ 30% improvement in pain intensity in 72 of the 104 patients, and 45 of these patients had maintained the study drug and efficacy for over 6 months (31 of these patients received IT monotherapy with ziconotide; 14 had combination therapy with morphine, bupivacaine or baclofen). This sustained result (significant improvement in VAS at one month through to 6 months) was statistically signficant (p<0.01) and no differences in the change in VAS scores were noted by diagnosis. No SAEs were reported. 66 of the 104 patients (63.4%) reported one or more AEs. AEs observed in >10% were characterised as: psychomotor disorders (34.6%) and asthenia (22.1%), balance disorders (20.2%), sensory impairment (15.4%), altered muscle tone (14.4%), and motor coordination disorders (12.5%). The typically reported AEs of "altered mood, confusion, memory deficit, abnormal CPK levels, vertigo, nausea" were recorded. 18.3% discontinued ziconotide due to AEs (6.7% for lack of efficacy, 5.8% for non-compliance, 3.8% for infusion system AEs). The authors conclude that IT ziconotide "might" provide relief of chronic, refractory pain and that the side effect profile "seems" acceptable, but they also call for further long-term studies to investigate these findings. The authors note the key limitations of the study, including the retrospective observational and non-controlled design, a lack of standardisation in treatment protocol and data collection, and missing data. This study provides low level evidence given the study limitations and possibility for bias in the results.

1-	RCT	169 ziconotide, 86 placebo	Randomised to either ziconotide or placebo. The dosing schedule was changed during the study to adjust for AEs encountered at the initial dosing scheme (starting: 9.6ug/day; maximum 168ug/day); the last 199 enrolled (130 of the 199 were randomised to ziconotide) received the lower dosing schedule (starting: 2.4 ug/day; maximum 57.6ug/day). Doses were increased at 24 hour intervals until either pain was controlled, AEs experienced, or the maximum dose was reached. After 6 days of the initial phase, responders were moved into the maintenance phase where the same intervention was continued. The nonresponders were moved into the open-label study and received ziconotide.	Clinical effectiveness of the intervention	Mean % change in VASPI score from baseline (at the end of the 6 day initiation phase).	At the end of the initiation / titration phase (6 days), "the ziconotide-treated patients had a mean percent VASPI improvement of 31.2% (95% confidence interval [CI], 24.6–37.9%) compared with 6.0% (95% CI, 0.0–11.9%) for the placebo-treated patients." (p<0.001) Subgroups analysed: "Initial dose (≤ 0.1, > 0.1 µg/hour), age (< 65, ≥ 65 years), sex (male, female), race (Caucasian, other), prior treatment with IT morphine (yes, no), pain syndrome (central, peripheral), and pain classification (neuropathic, non-neuropathic). There were no clinically meaningful differences in the percent change in VASPI score among the ziconotide treated patients for any of the subgroup analyses, with the exception of pain classification. Although not statistically significant, the ziconotide nonneuropathic pain subgroup (n = 22, 16.0% change in VASPI score) had an apparently lower response than did the much larger ziconotide neuropathic pain subgroup (n = 124, 31.6% change in VASPI score). The placebo	"Secondary efficacy measures included changes on the Category Pain Relief Scale (CPRS), the Wisconsin Brief Pain Inventory Subset (WBPIS), and the Global McGill Pain Score, from baseline to the end of initial titration, and the percentage of patients who met treatment response criteria. The mean percent change from baseline on the VASPI score during the maintenance phase and crossover titration phase and the percentages of treatment responders during the crossover titration phase were also evaluated. Opioid use was monitored daily and was converted to oral morphine equivalents using standard conversion factors for	"At the end of the initial titration phase, a significantly greater percentage of patients treated with ziconotide (33.7%) than placebo (12.8%) were responders to treatment (p < 0.001; CMH general association test stratified by center). Patients treated with ziconotide reported significantly greater pain relief on the CPRS than those treated with placebo (p = 0.001, Table 3). At the end of the initial titration phase, 43.8% of ziconotide treated patients expressed pain relief that was moderate or better, including 15 patients (8.9%) who experienced complete pain relief. Among patients receiving placebo, 73.3% felt no relief or a worsening of their pain and 17.4% experienced moderate or greater pain relief, but none reported complete pain relief. A statistically significant difference (p = 0.028) also was observed on the Global McGill Pain Score, where ziconotide-treated patients reported a mean 23.0% improvement compared with a mean 9.2% improvement for the placebo group. Ziconotide-treated patients reported a nearly significant (p = 0.057) greater improvement in sleep on the WBPIS than the placebo treated patients,	Wallace MS, Charapata SG, Fisher R, et al. Ziconotide Nonmalignant Pain Study 96-002 Group. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial.. Neuromodulation. 2006;9(2):75–86..	- The article notes that the study dosing protocol was changed during the study for lower doses as there were high rates of AEs with the initial (higher) dosing schedule. - Mean VASPI and mood scores at baseline were significantly different between the treatment and placebo groups. - 94.7% of ziconotide- and 72.1% of placebo-treated patients reported at least one AE (p = 0.001) durint initiation (mild to moderate: 78.3% ziconotide and 91.9% placebo), 24 (14%) ziconotide-treated patients discontinued the drug in initiation from AEs - 57 SAEs in 39 ziconotide-treated patients (84% ziconotide-related, 60% led to discontinuation, 45 SAEs in the initial titration phase) versus 3 SAEs in 2 placebo-treated patients - Ziconotide-related SAEs: 49% nervous system; most commonly reported were dizziness, confusion, urinary retention, nausea / vomiting, amblyopia or visual abnormalities, abnormal gait, stupor or somnolence, ataxia or vestibular disorders, and encephalopathy. - CK levels: 26 of 166 (15.7%) patients with initially normal levels were > ULN at termination, 9 had 3x ULN levels - "Comparison of ECGs did	The authors conclude, "Ziconotide demonstrated efficacy for the treatment of severe, chronic nonmalignant pain in a population of patients for whom conventional therapy, including IT opioids, failed. Ziconotide was effective when administered concurrently with systemic opiates and for patients with and without previous IT opioid experience. There was a considerable incidence of ziconotide-associated AEs due to the rapid titration and high doses administered. The narrow therapeutic window of IT ziconotide dictates a slower and more cautious titration, which is now incorporated in the U.S. product labeling."	This is a randomised controlled trial of IT ziconotide (169 patients) versus placebo (86 patients). The study population consisted of patients with mostly neuropathic pain (about 75% of study participants) of >1 year of duration (almost uniformly). Most patients were on oral opiods at baseline (ziconotide 73%, placebo 79%), and many had previously responded to IT morphine (ziconotide 50%, placebo 57%). Patient eligibility for the study required a baseline VASPI score of at least 50. Of note, the mean VASPI score at baseline in the ziconotide group (80.1) was significantly higher than the placebo (76.9) group and later statistical analysis was noted to account for this difference. The primary endpoint was set to be the change in mean VASPI score after the initiation / titration period (6 days). The study results showed a 31.2% improvement in mean VASPI score from baseline in the ziconotide group which was significantly (p<0.001) different from the placebo group's mean change of 6.0%. Stastistically significant imporovements versus placebo were also seen in the ziconotide group in terms of the reported Global McGill Pain Score (23% versus 9.2%), in pain relief reported on the CPRS, and in walking ability on the WBPIS. Finally, sleep improvement on the WBPIS improved in the ziconotide group with some, but not a 95% confidence, evidence of significant difference from the placebo group with a p = 0.0057. The authors conclude that ziconotide demonstrated efficacy in this trial, however, the predetermined definition of treatment response was set as a 30% improvement in mean VASPI score from baseline. While the mean improvement in VASPI score in the ziconotide group was 31.2%, the 95% confidence interval ranged from 24.6 to 37.9%. As the 95% CI included 30%, the arguement that the drug did not meet the primary efficacy endpoint exists. However, the authors reported a mean VASPI score improvement of 62.4% at the end of titration and 62.3% at the end of the maintenance phases for those patients that were randomised to ziconotide in the initiation/ titration phase and

						subgroups showed much more variability, presumably because of the smaller number of patients."	analysis." "Treatment responders were defined as patients having 1) a ≥ 30% improvement on the Visual Analog Scale of Pain Intensity (VASPI) compared to baseline, 2) stable or decreased concomitant opioid analgesics, and 3) opioid type unchanged from preinfusion if receiving opiates."	but placebo-treated patients reported a significantly (p = 0.010) greater improvement in walking ability than the ziconotide-treated patients." "For the patients initially treated with ziconotide who entered maintenance, mean percent improvements in VASPI score were similar from baseline to the end of the initial titration phase (62.4%) and from baseline to the end of the maintenance phase (62.3%). The patients who crossed over to ziconotide from placebo reported a mean 30.4% VASPI score improvement from baseline to the end of titration phase, and 26.9% of these patients were treatment responders. The 12 patients who responded to placebo and continued placebo treatment during the maintenance phase had a declining mean percent change in VASPI score from the end of initial titration (55.2%) to study termination (37.9%)." "Use of concomitant pain medications was similar between treatment groups. Among ziconotide treated patients, 94.7% received concomitant pain medications during titration, compared with 96.5% of patients on placebo; 79.3% of	not show any clinically important changes"		entered the maintenance phase as "responders." It seems, in this study, that the patients who did respond to ziconotide received an appreciable amount of pain relief (62% mean improvement in VASPI score), but this improvement was not consistent across the entire study population (31.2% mean improvement in VASPI score) and is not generalisable. The study was analysed on an intention-to-treat basis and reached numbers large enough to meet the power calculations. However, the dosing schedule change that occured during the trial was a major shift in the methodology (based on a high number of AEs) and represents a major limitation of this study. It is difficult to interpret the study results given this mid-trial protocol adjustment, but the safety (and narrow window) of IT ziconotide use is highlighted by this occurance. Indeed, 94.7% of ziconotide-treated patients had at least one AE (versus 72.1% in the placebo group, p = 0.001) during the initiation / titration phase, 78.3% of which were labelled mild to moderate in severity (versus 91.9% in the placebo group). Additionally, 57 SAEs in 39 patients were noted in the ziconotide group (veruss 3 SAEs in 2 placebo group patients) across the study duration. The authors note that 84% of the SAEs were related to ziconotide and 60% required a decrease or interruption in ziconotide dosing. The most common SAEs in the ziconotide group were: dizziness, confusion, urinary retention, nausea / vomiting, amblyopia or visual abnormalities, abnormal gait, stupor or somnolence, ataxia or vestibular disorders, and encephalopathy. Almost half (49%) of SAEs related to the nervous system, and in addition to the above included: agitation, catatonic reaction, abnormal thinking, depression, and aphasia. The study was also limited by its short duration. The short study period is insufficient to determine the safety and efficacy of IT ziconotide for patients with chronic pain in need of long-term intervention. Additionally, no significant change in oral opiod doses were noted, which may also reflect the short trial duration though this cannot be inferred.

								ziconotide treated patients, and 79.1% of placebo-treated patients used opioids. Opiate consumption did not change appreciably for either group during the relatively short titration period."				The efficacy of ziconotide is compared to placebo, not another IT intervention for pain control. The level of improvement felt necessary to be significant for an individual response was pre-set at 30%. Therefore, despite the 95% confidence that the mean VASPI scores improved by 24.6% to 37.9% in the ziconotide group, this result is of uncertain clinical significance as the group mean is not confidently above the individual 30% threshold. Overall, this study shows equivocal efficacy results and highlights the potential for adverse events and the narrow therapeutic window with IT ziconotide. Major limitations of the study design include the change in methodology mid-trial and the short duration of the trial, weakening the strength of evidence provided by this RCT.
3	Case series	3 patients	IT ziconotide (Dosing in 2 patients reported as "single 5- and 10-microg epidural test doses"; the third patient was on continuous infusion but the dose rate was not reported in the abstract)	Other	N/A	N/A	N/A	N/A	Wermeling DP, Berger JR. . Ziconotide infusion for severe chronic pain: case series of patients with neuropathic pain. . Pharmacotherapy 2006;26(3):395–402..	Single dose AEs: mild sedation, somnolence, nausea, headache, and lightheadedness. Infusion AEs: mild-severe ("depending on the rate of infusion") including sedation, confusion, memory impairment, slurred speech, and double vision	All 3 cases achieved pain relief	This publication reports on 3 patients with chronic neuropathic pain who received IT ziconotide. Two patients had complete (temporary) relief with epidural test doses and one patient had "considerable pain relief" with continuous IT infusion. AEs are reported, including mild AEs in the test dose patients and mild-severe AEs in the continuous injection patient. This provides very weak evidence. The full article was not reviewed.
3	Case series	7 patients	4/7 patients received ziconotide then combination therapy; 3/7 patients received only ziconotide; mean ziconotide initiation dose 5.2 mcg/d (range: 0.5 to 13 mcg/d) and mean last assessment dose 24.7 mcg/d (range: 0.06 to 146 mcg/d); mean duration of ziconotide 3.1 years (range: 26 days to 8 years)	Clinical effectiveness of the intervention	Efficacy and safety	Initiaion mean VAS score: 89.3 mm (range, 75 to 100 mm); mean decrease in VAS scores (at last assessment): 47.5% (range, 5% to 100%). AEs: urinary retention, depression, anxiety, and hallucinations	N/A	N/A	Kapural L, Lokey K, Leong MS, et al. . Intrathecal ziconotide for complex regional pain syndrome: seven case reports. . Pain Pract 2009;9(4):296–303..	N/A	N/A	This is a case series of 7 patients with CPRS given IT ziconotide (mono or combination) therapy. Efficacy and safety are reported. Duration of therapy and changes in VAS scores varied widely with a mean decreased in VAS scores of 47.5% (range: 5-100%) over a mean of 3.1 years (range: 26 days to 8 years) observed. AEs are also presented, including urinary retention, depression, anxiety, and hallucinations. This is a small case series which provides very weak evidence, but the specific CPRS population is noted. The full article was not reviewed.

1-	RCT	111 patients	Patients were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment. 5-6 day titration phase, then a 5 day maintenance phase for responders and cross-over for nonresponders Dose: 0.4 µg/h with uptitration every 12 hours (until maximum tolerated dose). This was lowered after the first 48 patients to 0.1 µg/h or less with uptitration every 24 hours (until analgesic effect or maximum of 2.4 µg/h). No other IT medications were allowed. Oral opioids were allowed.	Clinical effectiveness of the intervention	Change in VASPI score from baseline to end of titration phase	Mean VASPI score improvement (evaluable group): ziconotide 53.1% (95% CI 44.0%-62.2%) versus placebo 18.1% (95% CI 4.8%-31.4%), p<0.001, "with no loss of efficacy of ziconotide in the maintenance phase." Mean VASPI score improvement (ITT group): ziconotide 51.4% (95% CI not given) versus placebo 18.1% (95% CI 17.3%-49.4%), p<0.001. Moderate to complete pain relief: ziconotide 52.9% of patients versus placebo 17.5%, p<0.001. Responders (≥30% improvement in VASPI and no increase in opioid): ziconotide 50.0% of patients versus placebo 17.5%, p = 0.001.	Percent change in CPRS, WBPI, and KPSS scores, change in opioid use, response status, AEs were also monitored	CPRS score based pain relief: "moderate to complete in 52.9% of the ziconotide group (with 5 having complete relief) and in the same range but never reaching complete in 17.5% of the placebo group (P<.001). Responders: 50.0% ziconotide versus 17.5% placebo, p = 0.001 Opioid use: decreased 9.9% ziconotide versus increased 5.1% placebo	Staats PS, Yearwood T, Charapata SG, et al. . Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. . JAMA 2004;291(1): 63–70.	Titration phase: 22/72 (30.6%) ziconotide (31 SAEs, 14 were related to ziconotide and involved the nervous system) versus 4/10 (10%) placebo (4 SAEs). Most common SAEs (ziconotide group): confusion, somnolence, and urinary retention. "Nine types of adverse events occurred with significantly greater frequency in the ziconotide group compared with the placebo group...but starting at the lower dosage, using smaller dose increments, and increasing the interval between dose titrations tended to reduce this frequency" except for confusion. 7 cases of meningitis were reported. The authors comment on this that "the high rate of infection appears to be due to poor physiological status and presence of an externalized catheter, not to an idiosyncratic effect of the drug."	The authors concluded that IT ziconotide "provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS," while noting the significant vestibular effects from ziconotide use that were "easily recognizable and reversible." They also noted the decrease in AEs with lower starting dose and slower titration.	This is a well powered (n=111, 96% power, 5% significance level, 30% change in VASPI scores between the two study groups), randomised, double-blind, controlled trial of IT ziconotide in cancer and AIDS patients with chronic, refractory pain (VASPI scores of at least 50 at baseline measurment). Primary endpoint results analysed for the "evaluable" population showed a significant difference between the ziconotide and placebo group in terms of mean VASPI improvement (Ziconotide: 53.1% (95% CI 44-62.2%) versus Placebo 18.1% (95% CI 4.8-31.4%)) with p <0.001. Additionally, moderate to complete pain relief was reported significantly more in the ziconotide group than in the placebo group (52.9% versus 17.5%, p<0.001). The ITT analysis also revealed a significant difference in mean VASPI score improvement between the ziconotide and placebo groups (Ziconotide: 51.4% versus Placebo 18.1% (95% CI 17.3-49.4%, with a p<0.001. Only 5 patients reported complete pain relief in the ziconotide group. A statistically significant difference in the percentage of patients responding (defined as a 30% improvement in VASPI score, without an increased dose or change in type of concomitant opioid) to the randomised treatment was seen, as well (ziconotide 50% versus 17.5% placebo, p = 0.001). The authors conclude, that the study "revealed the considerable efficacy of ziconotide in patients with end-stage cancer or AIDS and with refractory pain. Ziconotide responders who entered the maintenance phase (n = 48, change in VASPI scores of 69.2%) seemed to sustain efficacy through that period (end phase change in VASPI scores of 69.4%). "The 26 patients receiving placebo who crossed over to the ziconotide group during the second phase experienced a 44.9% mean reduction in VASPI score at the end of the crossover phase. The 12 patients receiving ziconotide who crossed over to the placebo group experienced a 4.2% mean reduction in VASPI score at the end of the crossover phase." However, statistical significance was not reported. The study protocol was changed after the first 48

													patients were evaluated for safety in order to decrease the ziconotide dosing (0.1 µg/h or less to start, dose increased once per 24hours until pain control or 2.4 µg/h is reached). Compared with placebo, ziconotide was associated with a larger number of (typically dose-related) adverse events: abnormal gait, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea, and vomiting." The main limitations of this study are the short duration, the protocol dosing change mid-trial (though they note statistical significance for the primary endpoint was seen for both starting group subgroups), and some seemingly missing data which prompted a non-ITT analysis in addition to the ITT analysis of the primary endpoint (though no difference in result was demonstrated for this end point). Overall, this is a RCT of significant power which reached its primary end point, but the study's limitations weaken the potential strength of the evidence.
2-	Cohort	155 patients	Open-label IT ziconotide Dose note: During the first 12 months, "mean dose varied between 0.3 and 0.6 µg/hour; median dose varied between 0.2 and 0.3 µg/hour."	Clinical effectiveness of the intervention	Efficacy (mean VASPI percentage change from baseline in the study of origin)	Mean decrease in VASPI score (baseline to last observation): 36.9% (short-term trial, n = 144, 95% CI 30.1–43.7%, p< 0.0001), and the mean dose was stable in the 31 patients who participated over a year. Mean change at all time points was also significant (p<0.0001). Mean duration in study: 288 days (SE = 38.3 days; median = 86 days; range, 3–2047 days). Nonmalignant pain study origination: mean PDI score improvement at 1 month was 4.7 (SE = 1.92, n = 61, p = 0.0492), mean SIP-20 score improvement at 1 month was 1.9 (SE = 0.63, n = 61, p = 0.0027)."	Safety (AEs, labs, vitals)	- AEs: 147 / 155 patients (94.8%) ziconotide-related (often CNS involved), mostly mild or moderate, typically reversible with discontinuation or decreased dose - Discontinuation reasons: AEs (majority were related to ziconotide) 61/155 (39.4%), death (26/155, 16.8%), patient request (25/155, 16.1%), and lack of efficacy (24/155, 15.5%). - SAEs: 31 patients with SAE at least possibly ziconotide related (confusion, psychosis, anxiety, vestibular symptoms, dizziness, myalgia, overdose, and pain were n ≥ 2), 1 death was possibly related to ziconotide (66yo man with lung cancer died of aspiration pneumonia thought possibly related to the ziconotide, he had been on ziconotide for 531	Ellis DJ, Dissanayake S, McGuire D, et al. . Continuous intrathecal infusion of ziconotide for treatment of chronic malignant and nonmalignant pain over 12 months: a prospective, open-label study.. Neuromodulation 2008;11(1):40–9..	The authors note, "patient dropouts over time confounded the interpretation of the change and percentage change in VASPI scores at later time points in this study. There was an apparent increase in analgesic efficacy from month 3 to month 12 that resulted from a selection bias, because responders were more likely to stay in the study. However, post hoc VASPI score analyses performed on the cohort of 31 patients who remained in the study for ≥ 12 months (four with malignant pain, 27 with nonmalignant pain) enabled assessment of the potential for sustained effect...no attenuation of analgesic effect through month 12 (p < 0.0001)." The authors discuss the high attrition rate in the discussion section:	No evidence of tolerance	This is an open-label cohort study of 155 patients enrolled after responding to previous IT ziconotide in 1 of 2 study trials (both previous trials are reviewed separately in this CER, Staats 2004 and Wallace 2006). Efficacy outcomes revealed a 36.9% (SE 3.43) improvement in mean VASPI score from baseline until the last assessment (p<0.0001, n=144), and 45.8% (SE 6.8) mean change from baseline VASPI in the population remaining at 12 months (p<0.0001, n=31). Ziconotide-related AEs were experienced in 147 of 155 patients (usually mild or moderate in severity and reversible with dose decrease or discontinuation), and 31 patients had at least one SAE thought at least possibly related to ziconotide. No late-occuring AEs were noted. The authors report that over the long-term, doses remained stable. Limitations of the study include the open-label, nonrandomised design, lack of control / direct comparison group, the high attrition rate, and selection bias introduced (patients had already been observed to be "responders" to ziconotide in 1 of 2 previous trials). This study provides somewhat weak evidence. The authors concluded: "ziconotide can be a useful treatment option for a subset of patients with severe chronic pain who require long-term IT therapy."

								days). - CK elevated > 3x ULN in 19/145 (13.1%), 1 patient discontinued ziconotide due to elev CK (peak level 918 IU/L)		"The attrition rate due to death, AEs, and lack of efficacy was substantial in this study; only 31 out of 155 patients (20.0%) remained in the study for at least one year. Many factors may have been involved in this attrition, including the protocol requirement for ziconotide monotherapy and the enrollment of end-stage cancer patients and nonmalignant pain patients with complex medical and pain histories. In addition, several patients may have dropped out early because of the heightened side-effect profile observed with rapid dose escalation (23,24). Slower titration is associated with an improved side-effect profile and a much lower short-term discontinuation rate (33)."		

2+	Cohort	640 patients	Ziconotide titration, then long-term infusion (Dosing: maximum 100% increase per 12-hours, titrated to analgesia and AEs, mean dose at last infusion over first 12 months was 8.4 g/d, range 0.048 –240.0 g/d)	Clinical effectiveness of the intervention	Safety	- AEs: 99.7% had at least 1 AE, 91.1% were noted in first 14 days, 43.5% were mild, 42.3% were moderate, 58.6% unrelated to ziconotide, most common were nausea, dizziness, headache, confusion, pain, somnolence, and memory impairment; CK 3x ULN at 1 month in 5.7% and at discontinuation in 3.4%. - Discontinuation reasons: AEs (48.9%), lack of efficacy (29.7%), and rollover into a new ziconotide study (10.6%). - Median duration of therapy 67.5 days (range, 1.2–1215.5 days); 119 patients (18.5%) had 360 days; 36.6% had temporary interruption; total study exposure was 350.9 patient years - SAEs: 233 (36.2%) had ≥ 1 SAE, 56 (8.7%) had a ziconotide-related SAE (most common: confusion, mental slowing, stupor, and delirium)	Efficacy	Median VASPI scores: 76 mm (range 4–100 mm, SD 20.3, n=643) at baseline, 68 mm (range 0–100 mm, SD 27.7, n=453) at 1 month, and 73 mm (range 0–100 mm, SD 25.4, n=643) at last observation up to 2 months. "Among patients with VASPI scores 50 mm at baseline who completed 1 mo of therapy, 129 of 394 patients (32.7%) had a 30% improvement in VASPI score at month 1." Pain impact on daily life: baseline versus 2 months (p< 0.001, 35.1% improved versus 10.6% worsened) Work: Differed (p=0.0340) Driving: Differed (p=0.0004) Ambulation: No difference Sleep: No difference	Wallace MS, Rauck R, Fisher R, et al. Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial. Anesth Analg. 2008;106(2): 628–37. Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial.. Anesth Analg. 2008;106(2): 628–37.	N/A	No concern for withdrawal with abrupt discontinuation for SAEs	This is a large (n=644), open-label cohort study which aimed to evaluate the safety of IT ziconotide. Results showed 99.7% of participants with an AE and a high discontinuation rate due to AEs (61%, with 48.9% permanently discontinuing ziconotide due to AEs). Only 18.5% (119 patients) had 360 days of ziconotide in this study (the study median duration was 67.5 days), with AE being the main reason for discontinuation (followed by lack of efficacy in 29.7% and transition into another trial in 10.6%). "The AEs experienced by 25% of patients included nausea (52.6%), dizziness (51.6%), headache (40.1%), confusion (35.1%), pain (32.0%), somnolence (29.3%), and memory impairment (27.8%). Most reported AEs were described as either mild (43.5%) or moderate (42.3%), and more than half (58.6%) were considered unrelated to ziconotide. Those AEs considered ziconotide-related with the highest incidence were dizziness, nausea, confusion, memory impairment, and nystagmus." In terms of efficacy, 32.7% of participants with a baseline VASPI score of 50 or more (85.2%) had at least a 30% improvement at month 1. Improvement in pain impact on daily life scores was also seen in 35.1% at month 2 (P<0.001). Study limitations include the relatively short duration for a comprehensive safety report (which the authors point out is not likely long enough to detect rare AEs), lack of comparator / control, and the nonrandomised / open-label design. The authors conclude that "long-term IT ziconotide is an option for patients withsevere, refractory chronic pain. Overall, however, this study provides a moderate level of evidence for the safety of ziconotide.

2-	Cohort	78 patients	This was an "open-label, long-term, multicenter extension study" where initial dose was based on dose from prior study (adjusted as needed for analgesia / AEs at study visits not less than 24 hours apart and by maximum increment of 2.4 mcg/day (downward titration unlimited). Note on dosing from results section: "At the Initial Visit, the median dose was 6.48 mcg/day (range 0.00e120.00 mcg/day)."	Safety of the intervention	Safety	- Discontinuation: 33 (42.3%) completed study, 14 (17.9%) transferred to another ziconotide study, 11 (14.1%) patient request/withdrawal of consent, 6 (7.7%) death, 6 (7.7%) lack of efficacy, 4 (5.1%) AE, 1 (1.3%) noncompliance, 1 (1.3%) lost to follow up, 2 (2.6%) other. - New AEs: 71/78 (91%), 37 (52.1%) ziconotide related - New severe AEs: 50/71 (70.4%), 8 were both severe and related to ziconotide - New SAEs: 35 patients (44.9%), 141 new SAEs, complications of quadriplegia (death) and psychosis were the 2 SAEs at least possibly related to ziconotide	Efficacy	Initial visit mean VASPI scores: 55.6 mm (SD 28.74 mm) Termination visit mean VASPI scores: 58.9 mm (SD 27.30 mm) No evidence of increased pain over time; some VASPI mean score changes were significant from baseline	Webster LR, Fisher R, Charapata S, et al. Long-term intrathecal ziconotide for chronic pain: an open-label study. J Pain Symptom Manage. 2009;37(3):363–72. Long-term intrathecal ziconotide for chronic pain: an open-label study. . J Pain Symptom Manage. 2009;37(3):363–72.	Death due to complications from quadriplegia: possibly related to ziconotide; on ziconotide > 7 years, multiple complications / hospitalisations 7/71 (9.9%) developed a T wave inversion on ECG ("the significance of this abnormality is unclear")	- 47/78 (60.3%) continued until study end or transferred to another ziconotide trial, 4 discontinued secondary to AEs, 6 for lack of efficacy. - Mean VASPI improvement versus baseline: >10% at all but one time point (Day 60), >30% at two time points (Days 600 and 960)	This is an open-label, long-term (133.4 patient-years), cohort extension study of IT ziconotide in 78 patients who had completed 1 of 2 prior studies (Wallace 2008, Ellis 2008, both independently reviewed in this CER). 5% discontinued the study due to AEs, while 43% completed, 18% transferred to another ziconotide study, 8% discontinued due to lack of efficacy, 14% withdrew consent / left on patient request, 1% were lost to follow-up. 71 of 78 patients had new AEs, with 37 (52%) considered ziconotide-related and 50 (70.4%) considered severe in intensity. 8 AEs were considered severe and zicontoide-related. 35 of 78 patients had new SAEs (141 in total), with 2 at least possibly related to ziconotide:1) psychosis, and 2) complications of quadriplegia leading to death (the aritcle noted the investogator was "uncertain ofthe causality of the complications of quadriplegia that led to the patient's death" and the patient had been on ziconotide for over 7 years). Efficacy results showed no significant loss of pain control (per change in mean VASPI scores) over time, with some instances of improved mean pain control scores at various time points. However, pain improvement was not very impressive as there were only 2 points (days 600 and 960) where a > 30% improvement in mean VASPI scores from the baseline in the study of origin were noted (a > 10% mean improvement was noted otherwise, except for the Day 60 time point). This study is mainly limited by its post-trial / open-label, nonrandomised, uncontrolled / noncomparative study design. The authors conclude, "The results of this study suggested that long-term treatment with ziconotide was well tolerated and provided maintenance of stable pain intensity in this enriched sample of patients who were self-selected for response to ziconotide and for tolerating ziconotide well. No evidence of cumulative toxicity of ziconotide was noted." Overall, the results lend weak evidence for the efficacy and safety of IT ziconotide.

2-	Cohort	71 patients	Titration phase (all), then extension phase (if not eligible for an internal pump, but wanted to continue use with the external system). The initial titration phase was set to 3 weeks, then lengthened in Belgium for local insurance policies, then reduced everywhere due to meningitis rates. Dosing: initially 2.4 µg/day (0.1µg/hour), titrated for analgesia or AEs in increments of ≤2.4 µg/day (≤ 0.1 µg/hour) ≤2x/week and not more than 1x/24 hours, maximum dose of 21.6 µg/day (0.9 µg/hour).	Safety of the intervention	Safety (AEs, SAEs, vital signs, labs)	- AEs: 64 (90.1%) had 363 AEs during titration, 53 (74.6%) mild / 44 (62%) moderate / 33.8% severe, 16 patients (22.5%) discontinued ziconotide due to AEs, 43 (60.6%) with at least 1 AE related to ziconotide, ziconotide-related AEs in ≥ 10% were dizziness (31%), nausea (14.1%), infusion device-related AEs in ≥ 10% were device failure (18.3%), CSF leakage (14.1%), lumbar puncture headache (14.1%), and catheter-related complications (11.3%). - SAEs: 19 (26.8%) had 23 SAEs during titration, 10 (14.1% overall) of these 19 had a severe SAE (8 related to the surgical procedure, 4 related to the infusion device, and 1 was ziconotide-related asthenia/leg weakness). 5 patients (7.0%, 95% CI: 2.3–15.7%) had meningitis.	Efficacy (Percentage change in VASPI score from baseline to each week of titration, CPRS and CGI scores at end titration, and change in systemic opioids)	- "Patient responses on all efficacy scales indicated pain relief." - Median percentage improvement in VASPI scores: 11.0% ($p < 0.001$, mean 22.3%) at week 1, 32.6% ($p < 0.001$, mean 32.7%) at week 2, 31.0% ($p < 0.001$, mean 32.8%) at week 3, and 23.5% ($p = 0.005$, mean 29.1%) at week 4. - CPRS scale: 52.2% had moderate to complete pain relief at end-termination - CGI outcomeS: 53.6% had "good to excellent" pain control, 10.1% had "complete satisfaction," and 62.3% reported being "at least somewhat satisfied" - Systemic opiod use: unchanged or decreased from baseline during titration (weekly)	Ver Donck A, Collins R, Rauck RL, et al. . An open-label, multicenter study of the safety and efficacy of intrathecal ziconotide for severe chronic pain when delivered via an external pump. . Neuromodulation 2008;11(2):103–11.	N/A	The authors concluded: "When titrated via an external infusion system, ziconotide provided clinically meaningful pain relief to patients with severe chronic pain. More than half of patients experienced good to excellent pain control, and statistically significant improvement was noted within the first week of titration. There was a high rate of AEs; however, ziconotide-related AEs were consistent with those reported in previous trials. The study results suggest that a one-to two-week trial of IT ziconotide using an external infusion system may be sufficient to assess patient response. This study is limited by the small sample size, open-label design, and lack of control group. Future well-controlled, doubleblind studies in large patient populations are warranted"	This is an open-label cohort study of 71 patients for which IT ziconotide was given first in a titration phase, then in an extension phase. The duration of the titration phase was altered twice from the initial study methodology plans, first to accomodate local practice, then in response to a high rate of meningitis diagnoses. The authors also note that the study was initially designed for a larger population, but enrollment rates were not able to fulfill the initial set criteria. About 90% of patients experienced AEs (363 AEs), with 33.8% of severe intensity and 2 AEs reported in 10% or more of patients (dizziness 31% and nausea 14%). 26.8% of patients had an SAE, with 1 SAE being zicontoide-related (asthenia/leg weakness). There were 5 cases of meningitis and the titration period was shortened in response to these events. Despite 52% with "moderate to complete pain relief" (per CPRS) and "good to excllent pain control" in 53.6% (per the CGI), only 10% reported complete satisfaction (per CGI), and only 62.3% were "at least somewhat satisfied." Median percent change in opiod dose was unchanged from baseline at week 4. The median percent change in VASPI scores showed significant improvement at weeks 1-4 (week 1: 11%, week 2: 32.6%, week 3: 31%, week 4: 23.5%). Overall, this study affords weak evidence on the efficacy and safety of ziconotide.

N/A	Other	Random 200 patient samples from 3000 simulated patients; repeated 2000 times (results were stable with 2000+ replications)	IT Ziconotide (Dosing note: Base case used0.26mg/hr; sensitivity analysis ranged from doses of 0.15mg/hr to 0.45mg/hr) Note, I believe the intention was for "mg" to mean "µg."	Cost effectiveness	Cost effectiveness model results	The authors concluded the model was robust. Base case CE of ziconotide versus best supportive care (BSC) was £27 443 per QALY (95% CI £18 304–38 504) with average discounted cost of £112, 598 (ziconotide) versus £94,734 (BSC) and QALYs of 1.674 (ziconotide) versus 1.012 (BSC). Probability of cost-effectiveness at a WTP per QALY of £20,000 was 8.5%, 38% at a £25,000 threshold, 74% at a £30,000 threshold, and 92% at a £35,000 threshold. Sensitivity analysis was done for discount rates, time horizon, responder definition, pump-related assumptions, utilities, dose, and discontinuation rates. Dose was the most sensitive parameter.	N/A	N/A	Dewilde S, Verdian L, Maclaine GDH. . Cost-effectiveness of ziconotide in intrathecal pain management for severe chronic pain patients in the UK. . Curr Med Res Opin. 2009;25(8):2007–19.	N/A	The authors conclude: "Conclusions: Ziconotide may offer an economically feasible alternative solution for patients for whom current treatment is inappropriate or ineffective. The main study limitation is that some model inputs, mainly related to resource use, are based on assumptions or expert interviews."	This article discussed the results of a cost-effectiveness model for IT ziconotide versus "best supportive care" from a UK NHS perspective. The simulation model uses three studies from which to base the clinical assumptions for zicontoide (Rauck 2006, Webster 2008 and Wallace 2006, all of which are reviewed in this CER). A probabalistic sensitivity analysis was performed and the authors concluded the model was robust to most assumptions, noting the most sensitivity to the dosage of ziconotide and discount rates. The authors report a base case ICER of £27,443 per QALY with a 95%CI between £18 304 and £38 504. The sensitivity analysis showed variability in the ICER with ziconotide dosing assumption changes, ranging from a low of £15 500 (95% CI £8206–25 405) with 0.15mg/hr to a high of £44 700 (95% CI £30 541–62 670) with 0.45mg/hr dosing (from a base case rate of 0.26mg/hr). This model is limited by the reliance on several different sources of data as the basis for assumptions, the lack of long-term data from which to base model assumptions (the authors note a 3-year maximum to reference data), and the use of expert opinion as the basis for some assumptions. The potential for bias therefore, limits the strength of the results.
3	Case series	3 patients	Switching therapy from IT opiate to IT ziconotide (Dosing details were not reported in the abstract)	Other	N/A	N/A	N/A	N/A	Thompson, JC, Dunbar, E, and Laye, RR. . Treatment challenges and complications with ziconotide monotherapy in established pump patients.. Pain Physician. 2006;9: 147–152.	N/A	N/A	"This report describes challenges associated with the decision to convert established pump patients from intrathecal opioid therapy to Ziconotide monotherapy. Inadequate analgesia, adverse medication effects, and opioid withdrawal symptoms can precipitate a stressful situation that may be perceived as dangerous or threatening by patients who are predisposed to anxiety." This is a case series of 3 patients, therefore the evidence strength is very weak. The full article was not reviewed.

3	Case report	3 patients	IT ziconotide (dosing details were not reported in the abstract)	Safety of the intervention	N/A	N/A	N/A	N/A	Penn R, Paice J. . Adverse effects associated with the intrathecal administration of ziconotide. . Pain 2000;85:291–6.	N/A	N/A	"This clinical report describes the experiences of three patients with serious adverse effects associated with intrathecal ziconotide." This is a case series of 3 patients, therefore the evidence strength is very weak. The full article was not reviewed.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Nil
Updated search terms - Population	Pain
Updated search terms - Intervention	Ziconotide Prialt
Updated search terms - Comparator	Intrathecal opiates Opiates
Updated search terms - Outcome	N/a
Inclusion criteria	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	N/a
Exclusion criteria	General exclusion criteria
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. No relevant outcomes 4. Incorrect study type 5. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 6. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	N/a