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REVIEW ARTICLE

Ziconotide Monotherapy: A Systematic Review of Randomised Controlled Trials

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Abstract: ***Introduction*:** Chronic neuropathic pain is difficult to treat and is often refractory to most modalities of treatment. Ziconotide is a novel, potent, non-opioid, calcium channel blocking agent which has been shown in clinical trials to be effective in treating chronic neuropathic pain.

***Methods*:** EMBASE, MEDLINE, CINAHL Plus and Web of Science electronic databases were searched for English language studies. Reference sections of articles were examined for further papers and the manufacturer of ziconotide was contacted for further unpublished data. Three randomised controlled trials in ziconotide monotherapy were included and subjected to a random effects meta-analysis.

***Results*:** All three studies used the similar main outcome measure (visual analogue scale of pain intensity; VASPI) and were therefore comparable. A Jadad score was performed for each paper. Frequent serious adverse events (SAEs) were observed which resulted in two of the studies revising the protocol. The meta-analysis revealed a pooled odds ratio (responders on ziconotide vs. placebo) of 2.77 (95% CI, 1.37 to 5.59).

***Discussion*:** The results suggest that ziconotide is beneficial for pain reduction in chronic neuropathic pain. However, there remain some methodological issues that may call into question the validity of the results. It is evident that more work needs to be conducted to further validate the efficacy of ziconotide and to discover new areas of use.

Keywords: Ca^{2+} channel blocker, MVIIA, neuropathic pain, omega conotoxin, Prialt, SNX-111, ziconotide.

1. INTRODUCTION

Pain has been described by many people but perhaps the best accepted of these descriptions or definitions is the International Association for the Study of Pain [1] definition: '*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*' [2].

Pain can be further broken down into many classifications, initially into acute and chronic and further by intensity: mild, moderate or severe [3]. Whereas acute pain can assist the body in preventing on-going tissue damage, chronic pain serves no such useful purpose. If damage occurs to central or peripheral neurons, this leads to neuropathic pain.

Neuropathic pain, once established, is notoriously difficult to treat and is often refractory to most modalities of traditional oral analgesics and adjuvants. Owing to an ageing population and a rise in the incidence of chronic diseases such as diabetes and the commonly resulting diabetic peripheral neuropathy, neuropathic pain is becoming increasingly commonplace [4]. A survey of chronic pain in Europe shows that approximately 19% of patients across Europe and 13% of adults in the United Kingdom (UK) report chronic pain. Of these UK adults, 32% report experiencing severe pain. As many as 21% of these adults have suffered chronic pain for more than 20 years [5]. The burden of this pain on patients, families and carers is difficult to quantify. It has been suggested that the quality of life for people with neuropathic pain is considerably lower than that of chronic heart failure patients [6]. The burden is also similar in headache, depression and diabetes [7]. Neuropathic pain is an increasingly widespread issue and one for which more should be done [8].

Neuropathic pain can be identified by the presenting symptoms of burning, shooting, lancinating and/ or stabbing pain [9, 10]. The standard treatments for neuropathic pain are oral anti-convulsant medication such as gabapentin or pregabalin with the addition of tricyclic antidepressant medications such as amitriptyline as an adjuvant therapy. However, these drugs are not without their own side-effects and often the benefits are outweighed by intolerable adverse effects, rendering patients' refractory to first line treatments.

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It is at this stage that GPs refer patients to a pain clinic, although it has been noted in a survey that only 16% of chronic pain patients in the UK have seen a pain management specialist [5], so it is evident that it is only the fortunate few who may have recourse to such specialist help with their pain management.

Once seen in the pain clinic setting, often the first option is to try adding further classes of anticonvulsants and antidepressants on rotation. Eventually systemic opioids are introduced such as morphine either orally or in transdermal formulation. However, systemic opioids induced side effects are a problem and are not easily controlled with additional medications such as anti-emetics or laxative therapy. Excessive sedation due to large doses of opioids also massively impact on the quality of the patients' life. In addition to the effects of nausea and constipation, the increased risk of suicide and endocrine side effects make systemic opioids unappealing to many patients. Furthermore, most long term follow-up studies show long term opioid intake to have no clear beneficial effect on the pain [11]. If this line of treatment fails, then the next stage on the treatment algorithm would be the option of intrathecal therapy, should it be available in that geographical area. The intrathecal route has many advantages in that the equivalent or enhanced analgesic effect can be achieved at much smaller doses due to the drugs being delivered centrally into the cerebrospinal fluid (CSF) so aiding the bioavailability of the drug. As a result of smaller doses, the side effect profile may be beneficial to some patients, in particular enhanced vigilance. In addition, drugs can be delivered by this route where systemic inactivation may occur *via* the oral route or in the case of ziconotide where the drug has an inability to cross the blood brain barrier [12]. Intrathecal therapy involves implanting a catheter into the CSF of the spine which is then connected to an intrathecal pump implanted under the skin of the patient's abdomen [13]. Once the pump is implanted, the first drug of choice for many clinicians would be intrathecal morphine. The polyanalgesic consensus conference guidelines recommended, as first line intrathecal treatments, morphine, hydromorphone or ziconotide [14, 15].

The aim of this systematic review of randomised controlled trials was to establish the effectiveness of ziconotide monotherapy in patients with neuropathic pain. Furthermore, this article discusses the mechanisms of action of ziconotide, its benefits and side effects as well as the place of ziconotide in treating patients with chronic neuropathic pain.

1.1. Ziconotide

Ziconotide is the exact synthetic compound that corresponds to the toxin discovered in the fish hunting marine snail Conus Magus (or Magician's Snail), which is found in the Philippines. Baldomero 'Toto' Olivera was fascinated by the cone snails and was the first person to examine the effects of the snail's venom in the late 1960s, concentrating initially on the Conus Geographicus snail whose sting is so venomous it can kill an adult within hours. Olivera's investigations led him to the discovery that the snail venom contained powerful nerve toxins; however, he believed the toxins only mimicked the action of other known toxins and he left the research to return to molecular biology, almost abandoning the cone snail research. In the 1980s a student working in the laboratory with Olivera noted no reaction upon injecting the toxin into the peritoneum of rats. However, when he injected it into the rat's ventricle, a writhing movement was observed. The drug Ziconotide was born [16].

Ziconotide is a synthetic compound of the ω-conopeptide MVIIA derived from the Conus Magus fish hunting marine snail found in the Pacific Ocean. The molecule consists of 25 amino acids linked by three disulphide bridges folding the structure and producing the characteristic 3D structure critical for the activity as a Ca^{2+} channel blocker [3, 8]. The ω-conotoxin selectively binds to the N-type voltage-gated calcium channels found in the laminae of the spinal cord's dorsal horn. By binding with such accuracy, the influx of calcium is blocked and hence neurotransmission and modulation of nociceptive (defined as the neural processes of encoding and processing noxious stimuli) signaling is prevented, so hindering pain transmission messages arriving at the brain [3]. Ziconotide is the only selective N-type channel blocking agent currently approved for clinical usage [16, 17].

Ziconotide has advantages over morphine in that it has no interaction with the opioid receptors [9]. As a result, it can be demonstrated that there are none of the endocrine side effects common with morphine administration and tolerance does not occur [8, 17, 18]. In a case study of an opioid refractory patient who switched to intrathecal ziconotide, no signs of pharmacological tolerance, neurotoxicity or cardiovascular side effects were discovered [19]. In addition, it is important to realise how the lack of addiction, lack of withdrawal effects, opioid-induced hyperalgesia and other systemic effects common with morphine, are absent with ziconotide [20]. These factors have firmly placed it in the first line for the polyanalgesic guidelines in intrathecal drugs [14]. However, the uptake has been limited due to fear of side effects, the cost of ziconotide and the limited trialing options.

1.2. Side Effects of Ziconotide

Sites without the benefits of close support may be reticent about trialing ziconotide upon reading the Summary of Product Characteristics (SmPC) [21]. It states that in clinical trials, 88% of patient's experienced adverse events and although most were mild or moderate in severity, this figure is alarming. Among these side effects were dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), gait abnormality (16%), memory impairment (13%), blurred vision (14%), headache (12%), asthenia (13%), vomiting (11%) and somnolence (10%). The ziconotide molecule is large and hydrophilic, which contributes to the slow spread of the medication through the CSF to its target site in the dorsal horn of the spinal cord and subsequently results in slow onset of effect [17, 22]. Further evidence exists to show ziconotide cannot be given *via* the intravenous route as the drug has poor penetration across the blood-brain barrier, while producing profound orthostatic hypotension, sinus bradycardia, dizziness and nausea [17, 22]. Ziconotide is therefore only licenced for administration through the

intrathecal route and specifically with Medtronic SynchroMed® EL, SynchroMed® II Infusion System (Medtronic Inc., MN, USA) and in the CADD-Micro® External Microinfusion Device and Catheter (Smiths Medical MD, Inc., MN, USA) intrathecal drug delivery systems [8, 23]. A Field Safety Notice from Medtronic stated that only approved drugs for intrathecal use should be used in the SynchroMed systems, namely: floxuridine and methotrexate which are used as cytotoxic agents, baclofen which is used for spasticity and morphine and ziconotide which are used as analgesics [24]. Other analgesics such as clonidine, hydromorphone and bupivacaine are also used intrathecally but are not licensed for use in this route of administration. These medications can cause harmful interactions with pump materials causing pump stall and acute drug withdrawal. In addition to these factors, manufacturers do not license their pumps for combinations or mixture of medications such as ziconotide and morphine or other medications. This makes it more important than ever that ziconotide is used in a wider arena.

One of the greatest concerns in using ziconotide is the risk of suicidal ideation and psychosis [25]. The packaging information categorises psychotic disorders along with suicidal thought or attempt as 'uncommon' [26]. Certainly the consensus amongst clinicians is to be extremely wary of commencing ziconotide intrathecal therapy with any patient with a known psychiatric history or pre-disposition. Indeed, if there are any concerns regarding a potential patient's suitability for this particular drug at the author's hospital, a review with the Pain Clinic psychologist is arranged. The decision to treat would be made only following a full and thorough review within the multidisciplinary team to ensure the patient's safety. In addition, all patients are carefully screened at each clinic visit, whether it is during the refill procedure for the intrathecal pump or a routine clinic appointment for signs of confusion and for signs of psychiatric symptoms and any other side effects.

The ω-conotoxin MVIIA or ziconotide from the Conus Magus snail has one great advantage over other intrathecal medications in that the side effects are reversible, unlike the ω-conotoxin GVIA isolated from the Conus Geographicus snail – which binds itself so well to the N-type voltage sensitive calcium channel that it is virtually irreversible [8]. Therefore, should patients experience side effects from ziconotide, if the dose is reduced or discontinued; the side effects normally disappear within a few days to two weeks [9]. This then allows the clinician to further increase the dose. If the titration is performed on a slower titration schedule, patients can achieve higher doses of ziconotide without experiencing side effects. This virtue positions ziconotide as a valuable addition to the pain physician's armamentarium for treating patients with chronic neuropathic pain.

2. METHODS

Systematic searches of the electronic databases EMBASE, MEDLINE, CINAHL and Web of Science were performed using the keywords: ziconotide, omega conotoxin, MVIIA, Prialt, SNX-111, neuropathic pain. Databases were searched from their inception to 7th December, 2015. Additional search meathods included hand-search of the reference lists of relevant articles and consultation with experts. Additionally, we contacted the manufacturer of ziconotide, Eisai to enquire if further published or unpublished evidence was available. No further RCTs were identified by this route but the background data and additional open label studies provided have been used in the present work. The search was restricted to English language publications involving human participants.

Papers were included in the review if they met the following inclusion criteria: (1) randomised controlled trial design; (2) ziconotide administered as a monotherapy; (3) patients with chronic pain of neuropathic origin. Publications were excluded from the review if they met any of the following exclusion criteria: (1) articles were reviews, not presenting original research; (2) patients were receiving ziconotide mixed with other intrathecal medications; (3) patients with acute pain; (4) patients with nociceptive pain.

The selection criterion was applied to the citations identified by the literature search. An initial screen of titles and abstracts was conducted. Where selection criteria could not be determined from the abstract, the full paper of the citation was retrieved as were the full texts of all potentially eligible studies. Full text papers were examined for compliance with the inclusion and exclusion criteria. Quality assessment was performed and data was extracted from the studies meeting all of the inclusion criteria and none of the exclusion criteria.

3. RESULTS

Following removal of duplicates (n = 3) and removal of those studies not meeting screening eligibility criteria (n = 246), the full-text of 20 articles were assessed for eligibility. Five studies were excluded as ziconotide was mixed with other medications such as morphine [27-29], hydromorphone [30] or baclofen [31] and 11 studies were excluded because they were not RCT's [9, 10, 17, 32-34] or focused on the pharmacology of ziconotide [3, 8, 35-37].

Four RCT's were identified where ziconotide was used as monotherapy [38-41]. Of these four papers, an RCT of ziconotide use in acute post-operative pain following either elective total abdominal hysterectomy, radical prostatectomy or total hip replacement [38] was excluded due it not meeting the inclusion criteria. Three papers were included in this systematic review and in the meta-analysis (Fig. **1**).

3.1. Study Characteristics

One of the papers examined the use of intrathecal ziconotide in patients with cancer or Auto Immune Deficiency Syndrome (AIDS) who were experiencing refractory pain, or pain that did not respond to other therapies subject [39]. Out of the three RCTs this paper is the only one that refers to a specifically named disease, AIDS. The international charity for HIV and AIDS [42] states that neuropathic pain occurs in approximately 30% of people with AIDS. Another paper studied the treatment of chronic non-malignant pain [40] whilst the final paper focused on adults with severe chronic pain [41].

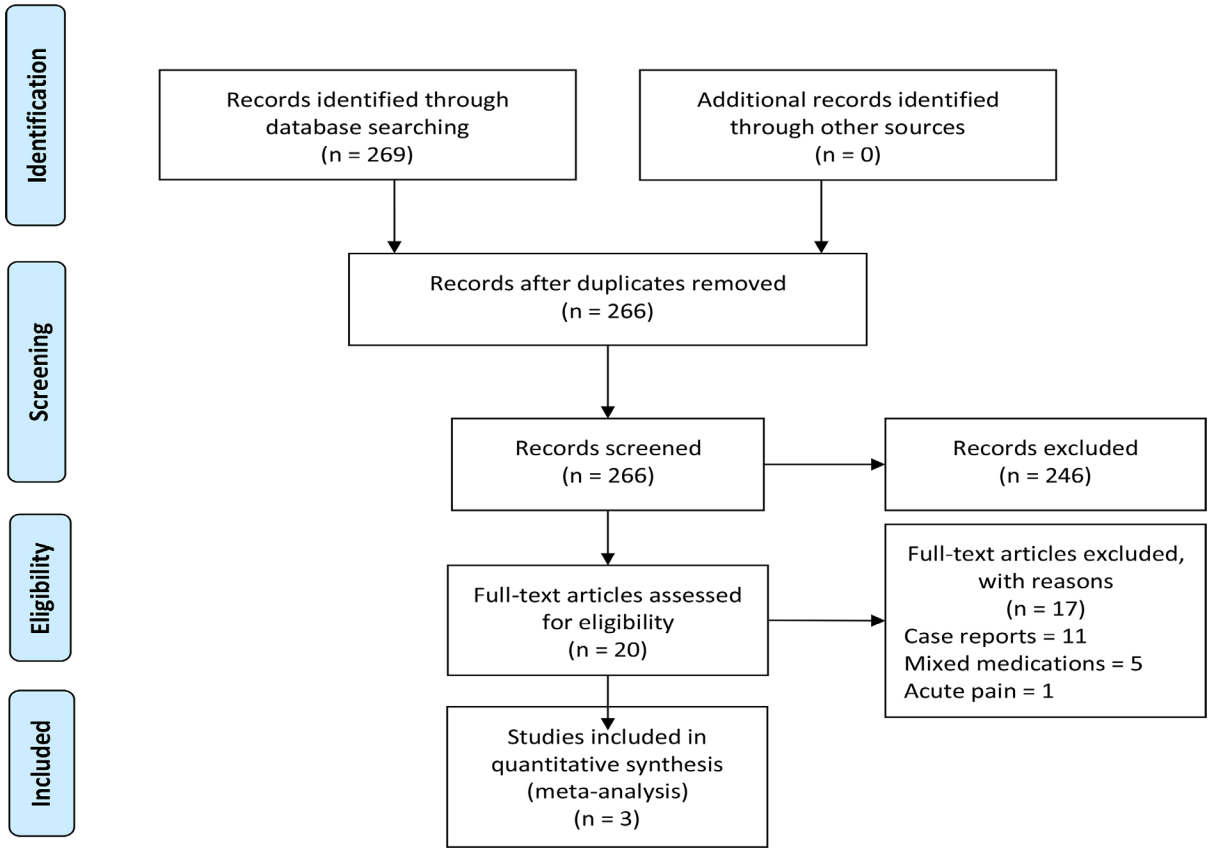

Fig. (1). PRISMA flow diagram detailing the literature search.

A total of 586 patients were included in the RCTs. with 349 receiving ziconotide and 234 receiving placebo. There is a small discrepancy of three patients from the stated numbers giving informed consent for study participation. It is not clear when reading the papers what happened to these three patients. Between all of the studies, 114 centres were involved, which can be broken down to show that study one recruited approximately three to four subjects per site [39], whilst the other two studies recruited five to six subjects per site on average [40, 41]. The study sites were located in the United States of America, Australia, Austria, Netherlands, Switzerland and Belgium. A comparison of the three studies can be seen in Table **1**.

3.2. Primary Outcome Measure and Definition of Responders

The primary outcome measure in each of the three papers was the Visual Analogue Scale of Pain Intensity (VASPI – also known as VAS). The VAS is a well-known and validated tool for pain assessment. However, it remains a very subjective method of pain measurement. Each study identified a responder as being a patient with ≥ 30% VASPI reduction at follow up (Table **2**).

3.3. Jadad Scale and Allocation Concealment

Each study was scored according to the widely used Jadad Scale [43] combined with the Concealment of Allocation scoring system [44]. The maximum score possible is five and indeed Staats [39] scored five out of five, and was also deemed to have adequate concealment of treatment allocation. Wallace [40] scored the lowest score with three out of a possible five with allocation of treatment rated as 'unclear'. Whilst Rauck [41] scored four with concealment of treatment allocation also deemed to be 'unclear'.

3.4. Randomisation

As mentioned above, only one paper reported the method of randomisation [39]. Both Staats and Wallace [39, 40] used a 2:1 randomisation ratio, with two patients receiving ziconotide to every one patient receiving placebo. On the other hand, Rauck [41] chose to randomise on a 1:1 randomisation ratio with each patient having an even chance of receiving either ziconotide or placebo. Although the authors did not advise as to the purpose behind a 2:1 randomisation ratio, it can be suggested that due to the nature of the disease or condition, AIDS or chronic pain, it would have been deemed unethical to have large numbers of subjects receiving placebo.

Staats [39] mention, in the study design section, that stratification occurred for each centre, by cancer or AIDS diagnosis and by history of intrathecal morphine use. When the demographic table is scrutinised it shows stratification probably occurred by gender also although this is not

Table 1. Study characteristics.

Author/ Year	Funding	Target Population	Sample Size	Number of Centres	Average Number Per Centre	Age Range	Randomisation Ratio	Study Group (n)	Control Group (n)	Primary Outcome Measure
Staats, 2004 [39]	*Neurex/ Élan Pharma Inc. and [†]Medtronic	Cancer and AIDS	111	32 in USA, Australia, Netherlands	3-4	24-85 yrs.	2:1 2- Ziconotide 1- placebo	68	40	VASPI
Wallace, 2006 [40]	Élan Pharma Inc.	Chronic non-malignant pain	255	43 in USA, Belgium, Australia, Austria, Switzerland	5-6	18yrs +	2:1 2 - Ziconotide 1- Placebo	169	86	VASPI
Rauck, 2006 [41]	Élan Pharma Inc.	Severe Chronic Pain	220	39 in USA	5-6	No specific age mentioned. Mean (SD)	1:1 1- Ziconotide 1- Placebo	112	108	VASPI

*Neurex merged with Élan Pharmaceuticals Inc. which then merged with Eisai. These companies manufacture ziconotide (Prialt™)
[†]Medtronic manufacture the Intrathecal Drug Delivery Systems – SynchroMed pumps that administer the ziconotide or other drugs.

Table 2. Definition of responders.

Author/Year	Definition
Staats, 2004 [39]	Responders had a 30% or greater decrease in VASPI scores, with no concomitant increase in opioid use or change in opioid class.
Wallace, 2006 [40]	Treatment responders were defined as patients having: A ≥ 30% improvement on the Visual Analogue Scale of Pain Intensity (VASPI) compared to baseline. Stable or decreased concomitant opioid analgesics and Opioid type unchanged from pre-infusion if receiving opiates
Rauck, 2006 [41]	Treatment responders were defined as patients with a 30% or greater decrease in VASPI scores from baseline to the end of week 3. All other patients including those with data missing at Week 3 were classified as non-responders.

mentioned in the write up as 34 men and 34 women were randomised to receive ziconotide against 20 men and 20 women receiving placebo. Wallace [40] and Rauck [41] do not report if stratification occurred during randomisation.

3.5. Study Design

In all three studies, there are three main phases: screening, titration and maintenance. The screening phase includes the period when patients who currently have intrathecal medications being infused *via* their implanted intrathecal pumps are gradually weaned and analgesia is maintained by increasing the systemic or oral analgesic medications prior to randomisation. The titration phase can be defined as the period where the dose of either ziconotide or placebo is gradually increased or titrated to a level where analgesia is obtained without side effects. When the optimum dose has been achieved, subjects move into the maintenance phase where the same dose is maintained until the end of the study.

3.5.1. Staats [39]

This study is double-blind, randomised and placebo-controlled in design. Within the body of the paper, no flowchart exists to demonstrate the study design to the reader. The authors of this systematic review have therefore attempted to design a flowchart from the paper (Fig. **2**).

The authors state that, prior to enrolment of research participants, institutional review board and ethics committee approvals were obtained and that written informed consent was taken from all participants in the study. However, it remains unclear at what time point the consent was acquired. Prior to this, it is mentioned that all intrathecal medications in the patients with implanted pumps were discontinued at least 3 days prior to study enrolment. This leaves the reader to wonder whether consent was obtained before intrathecal medications were discontinued or if this was a requirement to enter the study, as in the inclusion and exclusion criteria and consent was obtained at a later point? The International Conference on Harmonisation/ Good Clinical Practice guidelines (ICH/GCP), the European Clinical Trial Directive (2001/20/EC) and GCP Directive (2005/28/EC) [45] by which all research is governed, is very clear on the fact that no research activity or procedures should be conducted prior to written informed consent procedure having taken place (section 4.8.8). Likewise, the UK Medicines and Healthcare products Regulatory Agency (MHRA) would also view this as a serious breach of GCP as would the Food and Drug Administration (FDA) in America where the study was partly set.

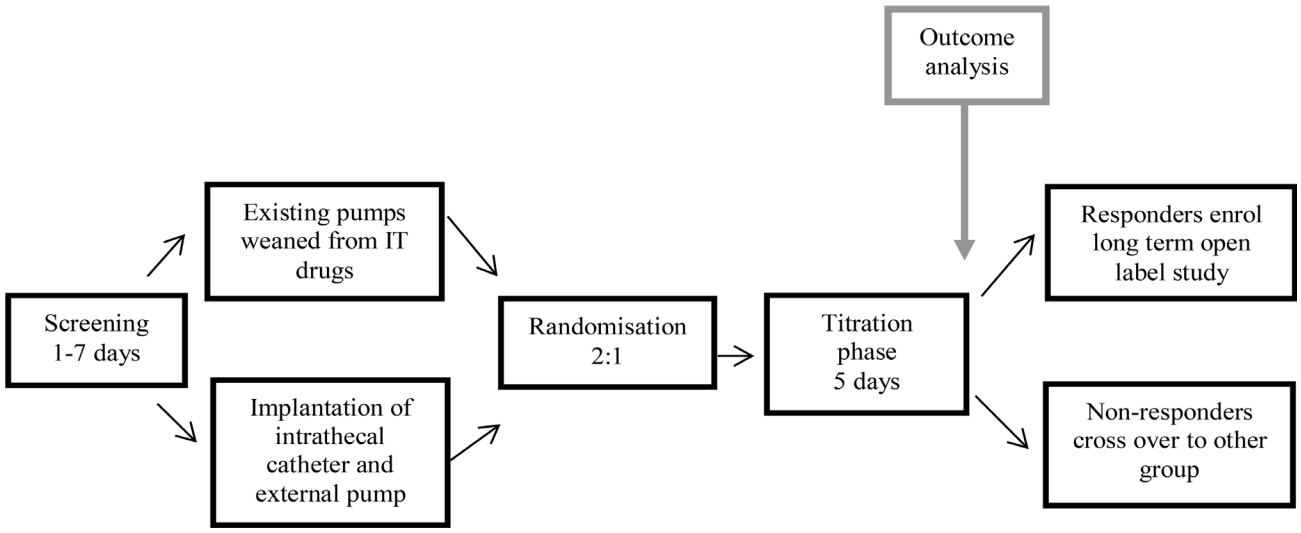

Fig. (2). Study design, Staats [39].

An initial screening phase and pre-infusion evaluation took place over one to seven days. For participants who did not have an intrathecal infusion device implanted, a catheter was placed in the intrathecal space and attached to an external infusion system. Due to the risk of infection and meningitis for patients having an external pump in situ, the authors limited the total time frame for drug infusion to two weeks for all patients. This is a valid point and the authors should be commended for its inclusion. Participants who already had an intrathecal pump in situ were weaned from the medications in their pumps. During this time, oral and systemic analgesics were maximised to manage their pain. The article does not clarify how this was achieved and one therefore assumes this was done as per each clinician's normal practice.

An initial titration phase lasting five days occurred following randomisation. At the end of this period, the investigators examined the data and ascertained who had responded to the treatment and who had not responded by calculating if they had achieved ≥ 30% reduction in VASPI scores. Responders were given an extra 5 days of maintenance therapy and the option to continue into an open label extension study. Non-responders were given a discretionary extra day by the investigator or an increase in dose if this could be administered. They were then given the option to cross over to the other treatment arm.

3.5.2. Wallace [40]

This study is a randomised, double-blind placebo-controlled trial. The authors provided a flowchart of the study (Fig. **3**) and clearly state that informed consent was taken prior to the performance of any study-specific procedures as per ICH/ GCP guidelines.

Following consent, subjects entered a screening period for one to seven days. During this time, the doses of intrathecal medications were titrated downwards and discontinued whilst simultaneously increasing oral and systemic analgesia. Subjects were stabilised on these for a minimum of three days prior to randomisation. Subjects were hospitalised for safety purposes and were monitored for 6 days on the blinded study drug. Following the double-blind phase, the VASPI scores were examined and subjects divided into either responders or non-responders. Responders entered the maintenance phase and received a further five days of blinded treatment as an outpatient. For non-responders, allocation concealment was broken and subjects receiving placebo were allowed to cross over to ziconotide treatment for five days. Those who were receiving ziconotide exited the study at this point. At the end of the study, all subjects who were deemed to be ziconotide responders were given the option of enrolling in an open-label extension study to continue treatment with ziconotide.

3.5.3. Rauck [41]

The third study [41] is described as a double-blind, placebo-controlled, two arm, randomised study (Fig. **4**).

As in Wallace [40], informed consent was obtained at the initial screening visit. Subjects were allowed a weaning period from other intrathecal medications of three weeks. At the same time, systemic opioids were increased for pain control before the subjects entered the stabilisation period of one week. The authors stated that the individual investigators at each site were allowed to use their clinical judgement and experience to wean patients. By this point, all subjects had their intrathecal pumps refilled with preservative-free saline. The authors describe patients not taking any IT medications as proceeding straight to the stabilisation period, however, should a patient have an intrathecal pump implanted, a drug infusion is required at all times, even if that is preservative-free saline, as otherwise the pump catheter becomes damaged and would need to be replaced. In the results section, it is stated that 44 patients entered the study with only saline infusion in their pumps. Unless the pumps were implanted just to enter the study and to obtain ziconotide during the pre-marketing phase, the only other reasoning is that perhaps the patients had failed other therapies and had the intrathecal drugs replaced with saline in their pumps.

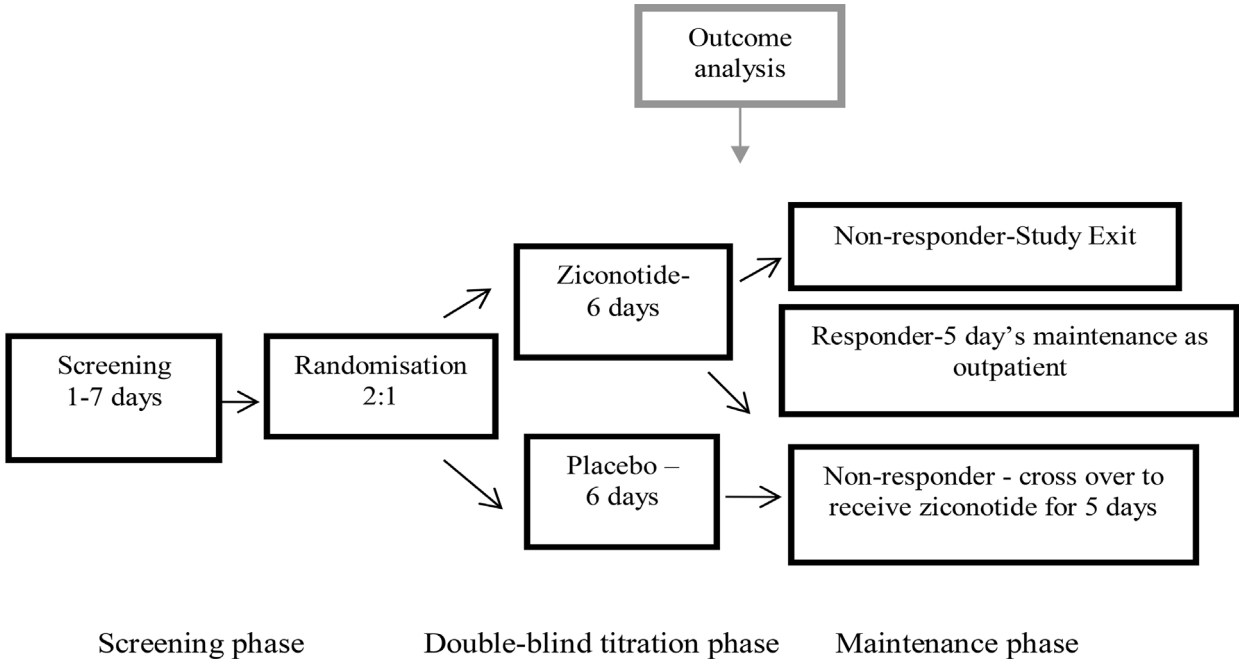

Fig. (3). Study design – Wallace [**40**].

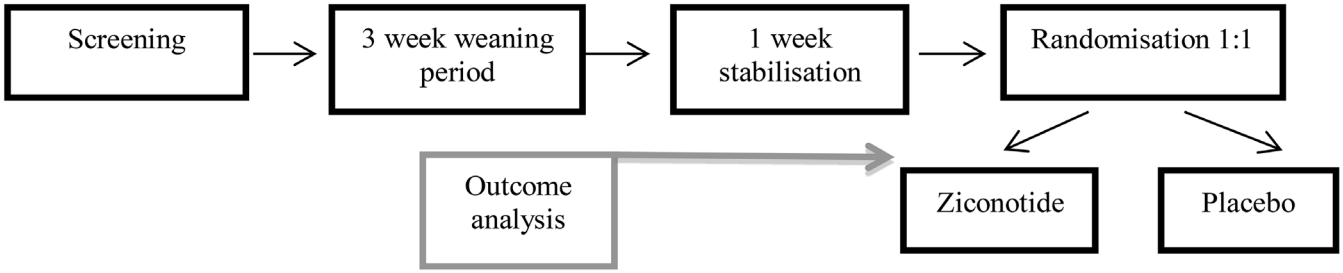

Fig. (4). Study Design – Rauck [41].

Randomisation took place following the stabilisation period. The double-blind period was conducted for three weeks as an outpatient trial. At the end of the three-week period, no mention is made by the authors as to whether subjects on placebo were allowed to cross over to receive ziconotide or to be given the option of an open-label extension study as in the other papers. It seems likely that they returned to their previous medications and those entering the study with saline in the pumps, were commenced on alternative intrathecal medications.

3.6. Ziconotide dose and Titration Schedule

The first two studies [39, 40] each state that the ziconotide used was an aqueous isotonic solution with a concentration of ziconotide 100mcg/ml with L-methionine and sodium chloride as excipients. Rauck [41] however, did not discuss the concentration of the drug used. Regarding the placebo, again, Staats [39] discusses the use of a placebo, as 'identical product' and Wallace [40] as 'identical except for the absence of the drug product'. Clarification was sought from the authors, who responded that the placebo was the drug carrier without the addition of the drug and was provided by the sponsor for the purposes of the study. Rauck [41] however mentions the use of preservative-free saline for patients entering the stabilisation period. Although the form of placebo is not clear, it is reasonable to assume that the preservative-free saline was used as placebo.

The starting dose of ziconotide in one of the studies was 0.4mcg/hr (9.6mcg/day); no maximum dose was set, apart from it being the maximum dose tolerated by the subject [39]. According to the protocol, upward titration was allowed every 12 hours. Similarly, the study by Wallace *et al.* [40] commenced at the same dose but placed a maximum dose at a cap of 7.0mcg/hr (168mcg/day). Upwards titration was allowed every 24 hours until analgesia was achieved, maximum dose or adverse events occurred (Table **3**). However, both these study groups encountered several adverse events and each had to submit a substantial amendment to their ethics committee to revise the protocol and reduce the starting dose to 0.1mcg/hr (2.4mcg/day). Both prescribed in the revised protocol a new upwards titration schedule of every 24 hours to maximum dose or analgesia, with Wallace [40] adding in 'or adverse events'. Both gave a revised maximum dose of 2.4mcg/hr (57.6mcg/day).

In contrast, Rauck [41] designed their study to evaluate the safety and efficacy of ziconotide on a slower titration

Table 3. Dose and titration schedule.

Author, Year	Starting Dose of Ziconotide	Maximum dose of Ziconotide	Titration Frequency	Dosing Schedule Amended	New Starting Dose of Ziconotide	New Maximum Dose of Ziconotide	New Titration Frequency
Staats, 2004 [39]	0.4mcg/hr (9.6mcg/day)	Maximum tolerable dose – no level set	Every 12hrs	Yes	0.1mcg/hr (2.4mcg/day)	2.4mcg/hr (57.6mcg/day)	Every 24hrs to max dose or analgesia
Wallace, 2006 [40]	0.4mcg/hr (9.6mcg/day)	7.0mcg/hr (168mcg/day)	Every 24hrs until analgesia, max dose or AE's	Yes	0.1mcg/hr (2.4mcg/day)	2.4mcg/hr (57.6mcg/day)	Every 24hrs until analgesia, max dose or AE's
Rauck, 2006 [41]	0.1mcg/hr (2.4mcg/day)	0.9mcg/hr (21.6mcg/day)	Min 24 hrs Increased by 1.2-2.4mcg/day	No	N/A – took lessons learned from other two studies and started at lower doses. Also much lower maximum dose than other two studies.		

schedule with lower maximum doses than Staats [39] as they identified that, although the subjects receiving ziconotide experienced clinically and statistically significant drop in pain scores compared to placebo, this came with a high rate of discontinuation due to serious adverse events (SAEs) and adverse events (AEs) [37]. Rauck [41] therefore learned from these previous studies and as a result commenced their starting dose at 0.1mcg/hr (2.4mcg/day). The maximum dose was also set much lower than in previous studies at 0.9mcg/hr (21.6mcg/day). The titration schedule was set at a minimum of 24 hours and subsequent doses were allowed at 1.2 – 2.4mcg/day increments.

Looking at the size of the doses involved in these studies, in the light of current thinking and knowledge on the subject, along with the authors personal experience from dealing with patients receiving ziconotide, the doses involved in the Staats and Wallace studies were huge. The Summary of Product Characteristics for ziconotide [21] suggests a starting dose of 2.4mcg/day titrated on an individual basis according to any adverse events and pain relief in increments of ≤ 2.4mcg/day up to a maximum dose of 21.6mcg/day due to the narrow therapeutic window in line with the Rauck study. The minimum interval between increments is quoted as every 24 hours but 48 hours would be preferable due to safety reasons. Extremely slow titration according to the patient's response should occur to limit the number of AEs and SAEs [10]. Approximately 75% of patients achieve a satisfactory analgesic response with a dose of ≤ 9.6mcg/day [21]. In the authors' personal experience, one patient who was involved in the original ELN92045-302 and ELN92045-352 studies has remained on a dose of 7.196mcg/day since 2005 with excellent pain relief. The highest dose in our practice is 12.751mcg/day.

Following the dosing schedule amendment in studies one and two [39, 40], the starting dose of 2.4mcg/day is more in line with current opinion; however, the maximum dose was still very high at 57.6mcg/day. The third study's [41] dosing schedule more closely mirrors current opinion on dosing with this potent novel analgesic. Nevertheless the titration schedule was extremely fast in Wallace [40]. Not only were patients commenced on a daily dose of 9.6mcg/day on the original titration schedule but the following day the dose tripled to 21.6mcg/day and from that point the dose was doubled every three days until 168mcg/day was reached. Following the revision of the protocol, the dose started at 2.4mcg/day – a more manageable level – although every two to three days the dose was doubled until an upper limit of 57.6mcg/day was achieved. This was of course carried out according to patient response. As can be seen from the comments above, this titration schedule was extremely rapid. In the authors' defense however, it must be said that the studies were conducted in the pre-marketing phase and the purpose of conducting studies is to define the optimum dosing and titration schedules amongst other things. Indeed, in his paper, Staats [39] states his patients were enrolled on the study between 1996 and 1998. We can examine the doses used in these studies with the knowledge we have today and with hindsight see that these doses were high and titration was probably too fast, but it is only through these studies that we have today's insight. Certainly Rauck [41] had learned by the previous studies and as such had altered the dosing in their protocol accordingly.

Decision to change the protocol occurred at different stages between the studies (Fig. **5**). Staats [39] had 48 subjects on the higher dose and titration schedule prior to changing to the new dose; thereafter 60 received the lower dose and slower titration. Wallace [40] decided slightly quicker that a change was required and the majority of their subjects received the new dose and titration schedule.

3.7. Adverse Events (AEs) and Serious Adverse Events (SAEs)

3.7.1. Staats [39]

During the initial titration phase of the study, the authors reported four SAEs with subjects in the placebo group and 31 SAEs in the ziconotide group. Of these 31, 17 were deemed to be not related to ziconotide. The remaining 14 involved the central nervous system with five reported as moderate in severity and nine as severe. The most common SAEs reported in the ziconotide arm of the study were confusion, somnolence and urinary retention.

Thirteen subjects died during the course of the study with a further two dying in the thirty day follow up period.

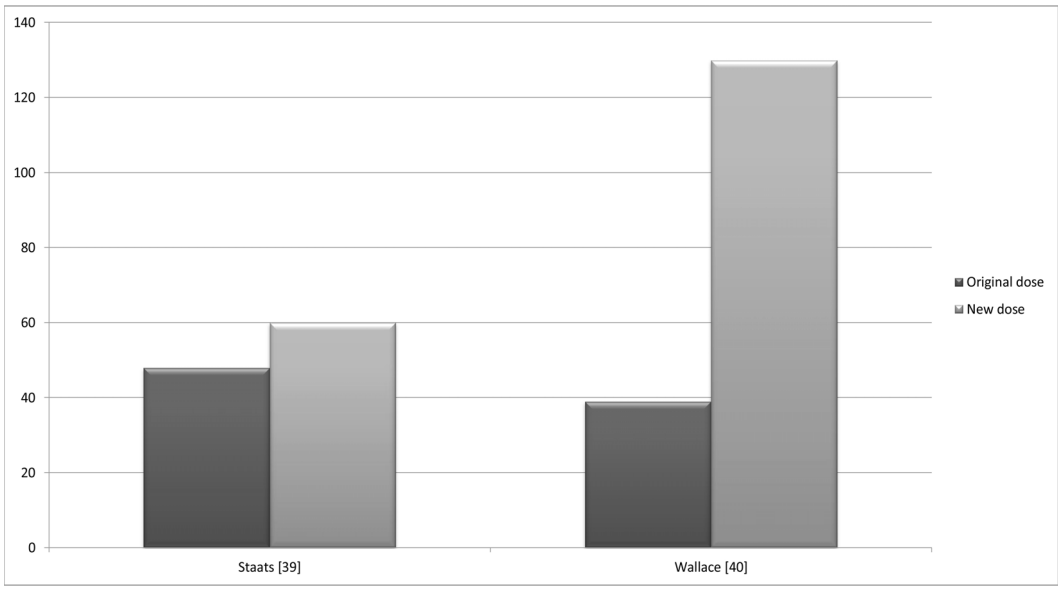

Fig. (5). Number of subjects on each titration schedule.

Twelve died due to cancer which is to be expected as the sample identified for the study included patients with cancer or AIDS. One died due to pneumonia, most likely AIDS related although this is not mentioned in the study, one was from unknown causes although this patient received placebo throughout the study, and the final patient committed suicide. Suicidal ideation and psychosis can result from treatment with ziconotide. However, although it is not mentioned in more detail in the article, it could equally have been suicide as a result of the diagnosis of cancer or AIDS or have been unrelated. It is therefore difficult to establish if this death was due to ziconotide or not. Five deaths occurred with subjects on placebo, two of these had crossed over from the ziconotide group.

Five patients contracted meningitis during the study. These were subjects in the ziconotide group and were all participants with external pumps in situ. It is a well-known risk when external pumps are utilised and the authors stated the study was designed to limit the drug infusion time to two weeks to reduce this risk.

Nine types of AEs occurred more frequently in the ziconotide group than in the placebo group. The investigators observed that starting on a lower dose whilst using smaller dose increments and extended intervals between titrations seemed to reduce the incidence of AEs. Not surprisingly, the authors noted that confusion occurred more often among participants who were older than 60 years of age.

3.7.2. Wallace [40]

Over the course of the study, Wallace [40] reported a total of 60 SAEs. These were broken down into 57 SAEs in the ziconotide group and three in the placebo group. Of the ziconotide subjects, 84% were deemed to be related to ziconotide and 49% involved the nervous system with 42% of these reported as severe in intensity. The commonest reported SAE was dizziness, followed by confusion, urinary retention, nausea and vomiting, amblyopia/visual disturbances, abnormal gait, somnolence, ataxia or vestibular disorders and two incidences of encephalopathy. All of these are known side effects of ziconotide and are listed in the summary of product characteristics. No patients died during this study.

Adverse events occurred in 95% of ziconotide treated patients and in 72% of placebo patients experiencing at least one AE. All were deemed to be mild or moderate in intensity.

One patient who had been randomised to receive ziconotide discontinued treatment due to a catheter dislodgement. A new catheter was implanted but the patient instead of being withdrawn from the study was then re-randomised to placebo. Following an inquiry to the authors, it was clarified that it was decided to re-randomise the patient for safety purposes. In clinical practice, should the catheter become dislodged, it is not always clear for how long the catheter has been dislodged. For safety reasons, the patient is usually titrated up from a much lower dose to ensure safety and to avoid AEs. In this case it is dubious as to whether the decision to re-randomise was in the best interests of the patient.

3.7.3. Rauck [41]

During the three-week treatment period a total of 44 SAE's were reported. Of these, 19 were in the ziconotide treatment arm with 25 in the placebo arm. It is unusual to observe considerably more placebo related SAEs than in the treatment arm. SAE causes reported were chest pain, hypertension, ataxia, dizziness and neuralgia. Of the SAEs reported 2% were study related in the ziconotide group and 2% study related in the placebo arm. One death was recorded during the study in a patient in the placebo group who had a history of chronic obstructive pulmonary disease and heart failure. This patient's cause of death was ventricular fibrillation. A summary of SAE's across all papers is shown in Fig **6**.

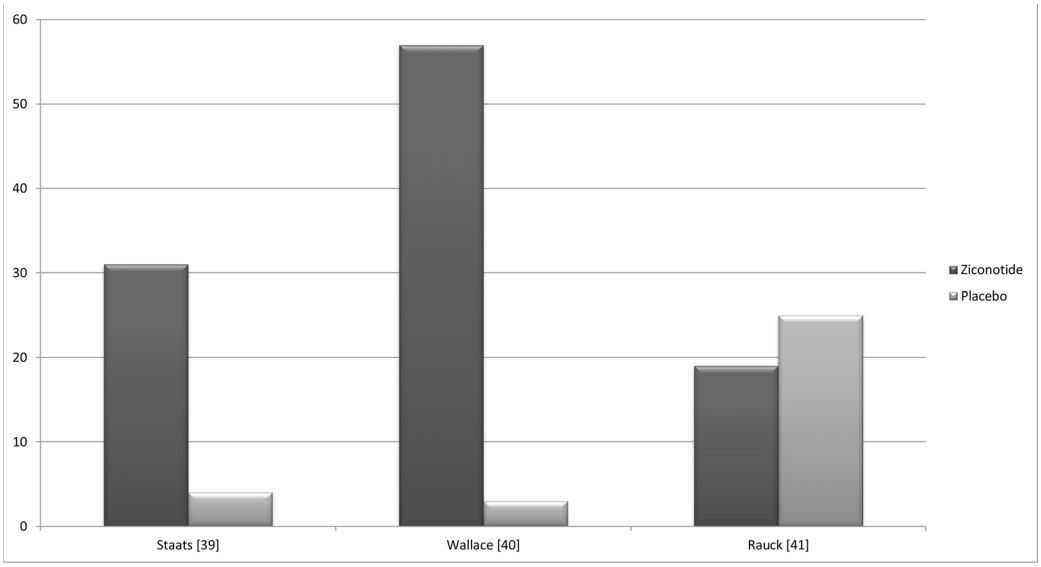

Fig. (6). Serious adverse events.

Adverse events during the treatment period occurred in 93% of the patients in the ziconotide group and in 82% of the patients in the placebo arm. All were reported as mild to moderate in severity. AEs reported all fell within the SmPC defined list of expected ziconotide AEs and were all related to the central nervous system (CNS) and included dizziness, confusion, ataxia, abnormal gait and memory impairment.

3.8. Study Management

3.8.1. Inclusion and Exclusion Criteria

Staats [39] list their inclusion criteria for the study as patients with cancer or AIDS with a mean VASPI of 50mm or greater during the three days prior to enrolment. Exclusion criteria listed twelve factors including dementia, untreated affective disorders, untreated infections and cardiac failure or bradycardia. Subjects were aged 24 years to 85 years old. Wallace [40] included patients aged over 18 years with severe chronic, non-malignant pain with a VASPI ≥ 50mm. Included participants were required to have an intrathecal pump implanted at study entry and to have demonstrated unsatisfactory response to systemic opioid therapy of at least two other treatment options. They excluded patients in the same categories as Staats [39] but specified that patients with a psychiatric disorder be excluded in accordance to the package leaflet warnings.

Rauck [41] included patients with severe chronic pain who demonstrated poor analgesic control by systemic or intrathecal analgesics with a VASPI ≥ 50mm. Subjects were required already to have an intrathecal pump in situ at study enrolment. Exclusion criteria included pregnancy or lactation, investigational drug use within 30 days prior to screening, known sensitivity to ziconotide and contraindications to intrathecal therapy. The authors in this study decided not to exclude coexisting medical or psychiatric conditions. The authors were aware of the box warning for severe psychiatric symptoms and neurological impairment as they mention it in their study, but they chose to avoid designating either as exclusion criteria. However, the investigators conducted the Mini Mental State Examination (MMSE) as part of their protocol and found no substantial changes in mental status of the patients.

3.8.2. Double-Blinding

Staats [39] discuss in their paper that a central call-in system was used to randomise patients into the study. Once in the study, sponsors, principal investigators and patients were not aware of the study randomisation. Only the pharmacists who prepared the study drug were aware of the treatment allocation. However, following randomisation, the patients' intrathecal pumps would need to be refilled with whichever study drug was allocated to the patient, be it ziconotide or placebo so the person carrying out this procedure would need to be aware of what was being refilled *via* the checks made during the refill. Even if this factor was blinded, the pumps need to be re-programmed following refill and it will be evident during this procedure what is infusing in the pump. Subjects would also require dose titrations and in this instance some people would have to be unblinded to the treatment allocation. It is extremely unlikely that the pharmacists would carry out the intrathecal refill procedure and titration programming so this means some other person or persons would need to be unblinded. It is not clear how treatment allocation was concealed during the study period.

Wallace [40] study team do not comment on blinded and unblinded team members; however they do mention that the titration was performed without breaking the blinding of allocation. They do not elucidate how this was achieved. One solution could be during the programming that all patients have the word 'ziconotide' entered as the drug name into the programmer (regardless if on placebo or actual ziconotide), the concentration could be entered as '25mcg/ml' and both groups could be titrated at the same flow rate with the exception that some were receiving ziconotide and some placebo. However, this may be speculation and the programming could have been performed differently. Rauck [41] on the other hand, commented that the study had a

three-week double-blind phase and titration was allowed but they do not enlighten the reader as to how this was done without breaking the blinding. It can only be speculated that for each study, unblinded study team members were involved in the refills and titration programming of the intrathecal pumps. The omission of this detail is a major limitation of all the included studies.

3.8.3. Protocol Deviations

Staats [39] indicate that there were no substantial violations to the protocol, which suggests that there were some protocol violations. However, one major protocol deviation can be identified, as there is mention of an open-label, compassionate use patient. Research subjects who have received medication that is still in the developmental phase (prior to Marketing Authorisation being awarded from the MHRA in the UK or the FDA in USA) should not be able to receive the drug at the end of the study. In this instance, the sponsor may provide the drug free of charge on a patient by patient basis until the Marketing Authorisation is obtained. This is described as "compassionate use". At the point this study was being conducted, the only way for patients to receive ziconotide was under the auspices of a clinical trial. However, this patient must not have fulfilled the inclusion and exclusion criteria or he would have been included in the study and this statement would not have been made. Moreover, this patient appears to have been included in the analysis of the results for the study. No more details are elicited in the paper regarding this matter. However, it can be claimed that by discussing this openly in the article, the authors were demonstrating transparency.

The protocol of the Staats study [39] defined responders as: having 30% or greater decrease in VASPI scores, with no concomitant increase in opioid use or change in opioid class. The authors separated out the responders into two groups, one group as 'protocol-defined responders' which consisted of 34 subjects receiving ziconotide and a further seven receiving placebo. However, they then describe how an additional 15 subjects were identified as responders by the investigators although they did not meet strict protocol-defined responder criteria. These extra 15 people went onto the maintenance phase of the study with the other protocol-defined responders. This would also be classed as a further protocol deviation. The protocol exists to ensure that all investigators are conducting the study in the same manner. If, however, investigators decide on their own volition that a subject is a responder and progresses the person onto the next phase of the study, then this could call into question the validity of the overall results of the study.

Wallace [40] and Rauck [41] have not declared any protocol deviations or violations and none were identified upon assessing the articles.

3.9. Efficacy of Ziconotide

In all three papers, the main outcome measure was the VASPI score. The mean evaluable group in Staats [39], show a statistically significant drop in VASPI by 53.1% (95% Confidence Interval [CI]: 44.0% to 62.2%) in the ziconotide group with 18.1% (95% CI: 4.8% to 31.4%) in the placebo group (P <0.001) (Fig. **7**). Five patients in the ziconotide group achieved complete pain relief with 50% of them responding to therapy compared to 17.5% in the placebo group (P = 0.001).

Wallace [40] also reported a statistically significant reduction of VASPI score. The ziconotide group had a mean percent VASPI improvement of 31.2% (95% CI: 24.6% to 37.9%) compared to the placebo group with a 6.0% improvement (95% CI: 0.0% to 11.9%).

Rauck [41] shows the proportion of treatment responders was not significant between groups (ziconotide: 16.1% and placebo: 12.0%, P=0.39). The effect size observed by Rauck [41] can be seen as much lower with the slower titration schedule.

Twelve placebo treated patients in the Wallace [40] paper fulfilled the criteria of treatment responders and entered the maintenance phase in the placebo group. This group had a

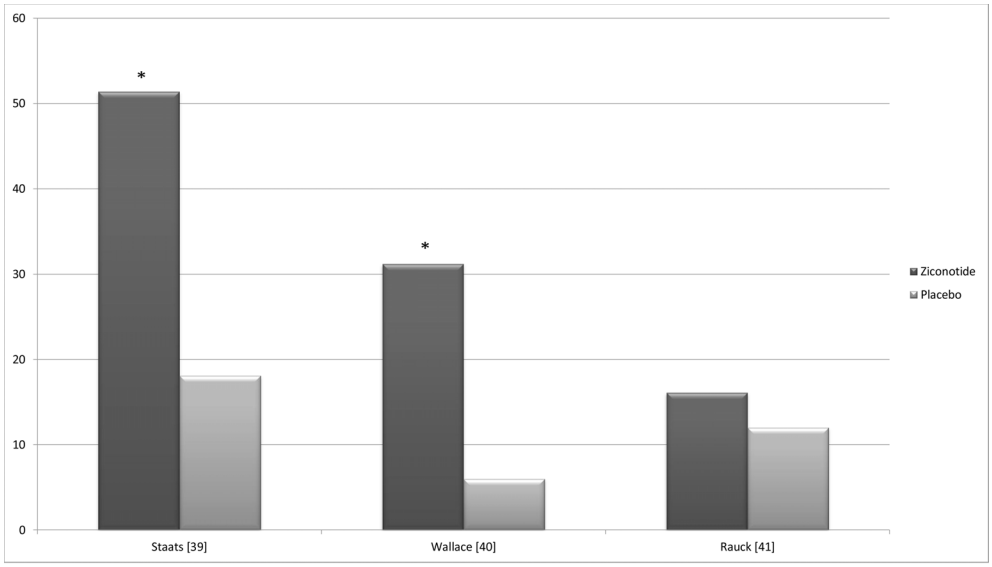

Fig. (7). Percentage change in VASPI score from baseline to end of titration period per study.

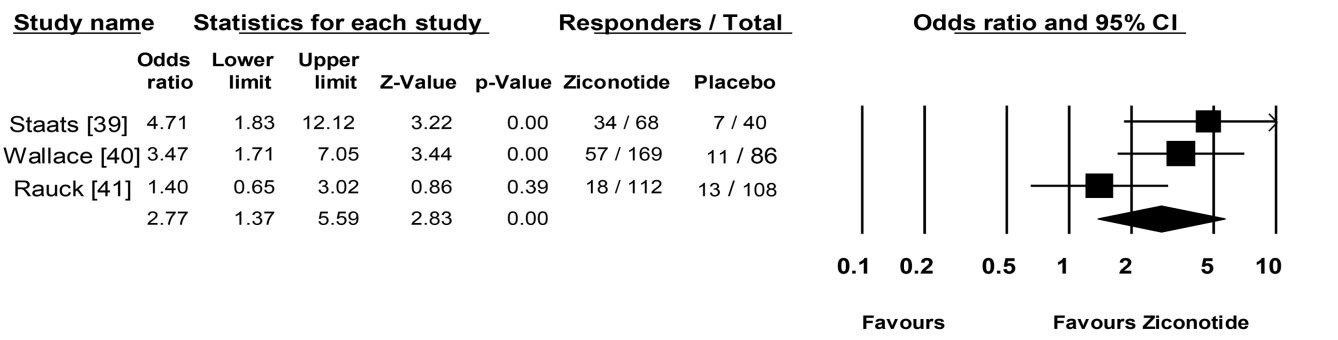

Fig. (8). Forest plot from a random effects meta-analysis of the effect of ziconotide on neuropathic pain.

slowly declining mean percentage change in VASPI score for the end of the initial titration to the end of the study. Their scores dropped from 55.2% to 37.9%. Evidently in this group of refractory chronic pain patients, any natural improvement in their symptoms is unlikely and as such they can be categorised as experiencing a placebo effect. This can be seen to be gradually reduced over the maintenance phase. Remarkably, a further phenomenon was noticed in the placebo treated subjects in a statistically significant improvement of walking ability than in the ziconotide arm ($P = 0.010$).

Data were analysed using Comprehensive Meta-Analysis Version 2.2.057 (Biostat, Englewood, NJ, USA). A random effects model was used based on the assumption that the true effect could vary from study to study. The pooled estimate (odds ratio) from this model is therefore the estimated average treatment effect from the distribution of study effects. The random effects model permits heterogeneity across studies to be modelled in the analysis.

The forest plot is shown in Fig. **8**. Heterogeneity was substantial with Cochran Q = 4.63 (P=0.10) and I2 = 57%. The I2 value indicates that 57% of the variability in treatment effect estimates is due to real differences between studies, with only 43% due to chance sampling variation. The confidence interval for the pooled treatment effect provides strong evidence that on average, ziconotide is beneficial for neuropathic pain relief. The standard deviation (SD) of underlying effects between studies (tau) was 0.47. This is the typical variability in the treatment effect from study to study. This random variability in effect between studies may be translated into a typical range for underlying treatment effects as ± 1 × tau, centred on the natural logarithm of the pooled odds ratio. The derived reference range for the odds ratio is therefore 1.30 to 5.89 (2.77 ×/÷ 0.47). A strong caveat here, of course, is that only three effects are included in the meta-analysis.

4. DISCUSSION

4.1. Study Limitations

The authors of this systematic review have worked with ziconotide for eleven years and during this time have seen successes and failures in treating patients. The best titration schedules were learned during the clinical trials. The authors have been involved in and experienced the drawbacks of ziconotide therapy with patients undergoing psychosis. A considerable amount of the patients treated have obtained excellent analgesia when all other medications were suboptimal for their requirements. However the authors have had patients for whom ziconotide was not effective. Ziconotide has much to offer and should be used on a wider arena. However, ziconotide is only suitable for a specific group of patients and as such; patient selection is a key point. Having used ziconotide in numerous patients the authors may have preconceived opinions of its efficacy and this could be perceived as bias.

The authors decided to use articles with ziconotide as monotherapy for the purpose of this systematic review as it was felt that this approach would provide a clearer analysis of this promising intrathecal medication. We recognise that there is a lack of recent RCTs or ongoing studies on this topic. The authors are also aware of a number of case studies and cohort studies with ziconotide however our pre-determined inclusion criteria precluded the inclusion of such studies and therefore only randomised controlled studies were included in this systematic review.

4.2. Methodological Considerations

Of the three studies included [39-41] two found statistically significant benefits of ziconotide versus placebo. Rauck [41] however reported no significant differences between the groups. However, the pooled effect from the meta-analysis shown in (Fig. **8**) reveals that ziconotide is beneficial in the treatment of neuropathic pain - with the estimate of the average overall effect suggesting substantial benefit (odds ratio approaching 3).

The refrain of 'start low, go slow' in the dosing and titration schedule with this calcium channel blocking agent is an important message [20, 23, 46]. This point was taken further in the consensus statement regarding the present suggested titration for Prialt (ziconotide) by proffering the recommended starting dose of not more than 0.5mcg/day, titrating upwards by increments of not more than 0.5mcg/day no more than once a week [47]. Interestingly, two of the

authors of this consensus statement were involved in the Staats [39] study, the same two authors were also involved in the second study group [40] and a further three authors in the final study group [41]. It should also be noted that three authors (Mark Wallace, Steven Charapata and David Ellis) all took part in each of the three studies. Five authors took part in two of the studies (Peter Staats, Robert Fisher, Michael Byas-Smith with Martha Mayo and Dawn McGuire who were employees of Élan Pharmaceuticals Inc) and five of these (Peter Staats, Robert Fisher, Michael Leong, Michael MineHart and Lynn Webster) were also involved in the consensus statement. This gives further evidence that the people involved in the study and consensus statement were experienced in the use of ziconotide.

There is evidence to show clinically important and statistically significant results in the differences in pain scores from baseline to the end of the titration phase [39, 40]. These papers illustrate a learning curve that was experienced by their authors in the dosing and titration schedules for ziconotide. Others learned by the high rate of serious adverse events (SAEs) experienced in earlier studies [39, 40] and amended their dosing schedule accordingly [41]. Indeed, the manner in which they titrated the intrathecal ziconotide with their patients concurs with the current SmPC and latest consensus of opinion. A lower rate of AEs can be demonstrated with smaller starting doses of ziconotide and careful titration [29]. This dictum can be heard reverberating around the walls of all centres currently using ziconotide. Nevertheless, when the dose is commenced on a low dose and gradually increased, it will have the major side effect in that analgesia will be suboptimal until a therapeutic dose is obtained. This usually begins (patient dependent) around 6mcg/day. Patients need to be informed of this fact and prepared that analgesia will not be obtained immediately but may take several weeks to achieve a dose that impacts on their pain. In discussing this factor with patients, it is also worthwhile to talk about the balancing of benefits against side effects and the hoped for eventual outcome of analgesia in the long run.

4.3. Advantages of Ziconotide

Examining the overall advantages of ziconotide we see many factors in its favour. Patients who have been receiving intrathecal morphine therapy have a high incidence of hyperalgesia [32], tolerance and rapidly spiralling higher doses along with the possibility of granuloma formation leading to potentially serious neurological conditions such as spinal cord compression. The endocrine side effects such as loss of libido, falling testosterone levels in men and risk of spinal osteoporosis [48] combined with hypogonadotrophic hypogonadism and amenorrhea or irregular menstrual cycles do not make intrathecal morphine a particularly attractive choice for the younger patients or those of a reproductive age [49, 50]. However, as has been shown in this work, ziconotide patients do not suffer from these side effects and Vitale [20] holds that ziconotide is the only drug of choice for this subset of patients.

In addition to the above benefits, the reversibility of the mode of action without withdrawal, is a valuable asset in the world of pain management [8, 51] and although a wide range of adverse events or side effects can occur with this drug, the majority are central neuropathic system orientated and cause minimal cardiovascular or respiratory complications [8]. Once the dose is down-titrated, the adverse event will usually resolve within a few days to two weeks and the dose can then be up-titrated at a slower rate to achieve analgesia at a higher dose. Therefore, careful monitoring of the speed of titration is vital. Furthermore, when the dose of ziconotide is reduced, no withdrawal effects are experienced by the patient. This is in stark contrast to morphine where withdrawal is a major issue [20].

Intrathecal morphine monotherapy may not be the optimum drug of choice for patients experiencing chronic neuropathic pain and intrathecal ziconotide may be more appropriate [17]. Ziconotide could be a valuable option for this group of patients who are often refractory to other forms of medication therapies.

Many patients labour under the stigma of receiving opioid treatment in whatever format that may be. The general populations are inclined to consider people taking morphine to be on an end of life pathway, or regard them, harshly, as abusers of opiate drugs. However, the same people would have no compunction in taking an ACE inhibitor for hypertension or antibiotics for a chest infection. As ziconotide is not classified as a controlled drug, it is not associated with this stigma of narcotic abuse. Patients and their families may therefore find this a more acceptable option [37].

4.4. Drawbacks with Ziconotide

One author advises how detailed patient selection is essential and it is recommended that ziconotide should only be for those people who are refractory to other systemic therapies and strongly advises against treating any patient with a known psychosis or history of psychiatric disorder [10]. Others agree and go on to suggest that there is an increased risk of suicidal ideation, hallucinations, paranoid reactions and manic reactions with ziconotide [51]. They allude to the fact that any pre-existing psychiatric disorders increase the risk of the above reactions to such a degree that it may exclude some patients from receiving ziconotide.

Ziconotide can be demonstrated to have a very narrow therapeutic window [8, 23, 29]. This fact, plus the long list of side effects and other issues to be taken into consideration such as psychological issues, means that it is recommended that ziconotide should only be used by clinicians and physicians experienced in intrathecal use [10, 19, 21].

4.5. Implications

NHS England have issued a policy stating that ziconotide is not routinely commissioned for use in severe refractory chronic pain [52]. The reasons behind this ruling are that there is no validated selection process for suitable patients, and the added complication of the only possible administration being *via* the intrathecal route. The evidence summary also suggests that there is not enough data to show cost effectiveness.

Ziconotide is only suitable for a small proportion of the chronic pain patients seen in the pain clinics and should not be seen as a panacea. However, perhaps more centres should be encouraged to trial ziconotide with their patients. Currently, only two centres use ziconotide, Middlesbrough and Leeds. This leaves the rest of the United Kingdom with nowhere for patients to go to receive this apparently valuable addition to the list of medications available. This means that the two centres are all based in the north of England with no availability for patients elsewhere in the UK.

4.6. Lessons to be Learned

We have shown that the only three randomised controlled trials using ziconotide monotherapy [39-41] have many commendable recommendations. However, there were points identified during the critical appraisal that require further explanation. Unfortunately, only one of the corresponding authors was able to respond to queries and many aspects remain unanswered. Certainly there is cause for concern in many areas of each of the three papers. Although the first paper scored the highest on the Jadad score, this quality was not borne out by the findings during critical analysis of the paper. However, two of the three studies were able to show a statistically significant outcome with reduction of the VASPI scores.

We must now learn from these early studies and follow the advice laid down by many [14, 15, 21] and follow the 'start low – go slow' mantra espoused by all who have had experience with this potent analgesic. Further randomised controlled trials into ziconotide are urgently needed not only to further the body of evidence into the interesting intrathecal medication, but to provide a safe environment for centres to assess the drug within the controlled auspices of a clinical trial. However, the authors strongly recommend that ziconotide should be used in centres with experience in early detection of side effects and in management of adverse events. In light of the NHS England commissioning statement [52], studies examining the cost effectiveness of ziconotide are also essential. Further studies might also examine other diseases and conditions that may benefit from its use and to identify other patients whom the Magicians snail can help.

Morphine, hydromorphone and ziconotide are suggested as being '*a priori'* equivalent except in the case of neuropathic pain and then ziconotide should be considered as first choice [12]. Ziconotide seems to be clinically effective in neuropathic pain of malignant and non-malignant nature. All that remains is for clinicians to learn to tame the magician.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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