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Emmanuel Bäckryd

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Do the potential benefits outweigh the risks? An update on the use of ziconotide in clinical practice

Emmanuel Bäckryd[1]

[1]Pain and Rehabilitation Centre, and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

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Corresponding author:

Emmanuel Bäckryd
Pain and Rehabilitation Medicine
Department of Medical and Health Sciences
Linköping University
SE-581 85 Linköping
Sweden
E-mail: emmanuel.backryd@regionostergotland.se
Phone: +46-(0)10-103 3661
Mobile phone: +46-(0)733-401 301
Fax: +46-(0)10-103 3682

Abstract

Background and objective

Ziconotide is a selective and potent blocker of N-type voltage-gated calcium channels. It was approved by the Food and Drug Administration in 2004 and by the European Medicines Agency in 2005 for the treatment of severe chronic pain in patients needing intrathecal analgesia (ITA). The aim of this paper is to provide a practitioner-oriented, educational, narrative, up-to-date review on the use of ziconotide in clinical pain medicine. Of special concern regarding safety is the partial incongruity between dosing statements in the Summary of Product Characteristics and novel low-dosage, slow-uptitration recommendations.

Material and Methods

Narrative review.

Results

Even though ziconotide has obvious advantages compared to opioids, pain practitioners pondering the use of ziconotide nonetheless have to balance its proved potential analgesic effect against its neurological side effects, with special consideration being given to dosing and neuropsychiatric dangers. Using a seesaw analogy, the paper discusses what factors pain physicians should weigh in when considering ziconotide as ITA drug, the non-opioid advantages of ziconotide being counterbalanced by its potential psychiatric side effects.

Conclusions

Ziconotide is an important part of the armamentarium of modern interventional pain medicine. If ITA is deemed necessary, ziconotide is a rational alternative, at least in chronic (neuropathic) non-cancer pain. However, in many European countries, ziconotide treatment is only available in a few (if any) centers. The safety profile of ziconotide is not fundamentally more worrying that that of opioids or cannabinoids; it is just different.

Significance: This paper provides a concise, up-to-date and clinically-oriented summary of the use of ziconotide in clinical practice, not least concerning safety and dosage issues.

Key words: conotoxin; dosage; intrathecal; non-opioid; psychosis; pump; suicidality; spinal; toxin; ziconotide.

Background

Research on the potential pharmacological use of venom-based medicinal products is ongoing (Gorson and Holford 2016; Netirojjanakul and Miranda 2017). Most drugs used in western medicine have a natural origin, and animal venoms have in recent years emerged as an important source of potential new drugs (Robinson et al., 2017), e.g. in the field of pain medicine where toxins from snakes, spiders, or marine snails are being investigated (Diochot et al., 2012; Rigo et al., 2017).

In 2004 and 2005, respectively, the synthetic conotoxin ziconotide was approved by the Food and Drug Administration and by the European Medicines Agency for the treatment of severe chronic pain in patients needing intrathecal analgesia (ITA) (Schmidtko et al., 2010). Ziconotide is a synthetic version of the hydrophilic conotoxin ω-MVIIA from the venom of the Pacific fish-hunting marine snail *Conus Magus* (Lyseng-Williamson and Perry 2006).

Ziconotide is a selective and potent blocker of N-type voltage-gated calcium channels (VGCC). Its analgesic effect is thought to be mediated by blockage of presynaptic VGCC on primary nociceptive afferents in Rexed laminae I and II of the dorsal horn, leading to subsequent lessened release of pronociceptive neurotransmitters and neuropeptides (Pope et al., 2017; Schmidtko et al., 2010). Although ziconotide is a first-in-class drug in virtue of being a *blocker* of VGCC, the well-known gabapentinoid analgesics gabapentin and pregabalin *modulate* the same VGCC by binding its accessory $\alpha_2\delta$ subunit (Burgess and Williams 2010; Patel et al., 2017a), suggesting that combining oral gabapentinoids with intrathecal ziconotide might perhaps be of value (Patel et al., 2017a).

Ziconotide is a highly hydrophilic 25 amino acids polypeptide with a molecular weight of 2639 Da, making it 10 times “bigger” than the alkaloid morphine (Miljanich 2004; Pope and Deer 2013; Web References 1 and 2). Being rapidly degraded by peptidases when it reaches the systemic circulation, ziconotide has to be infused directly into the cerebrospinal fluid (CSF), where its median terminal half-life is about 4.5 hours (Schmidtko et al., 2010; Wermeling et al., 2003).

For many years, morphine was the gold standard for ITA. Despite the widespread off-label use of other opioids, local anaesthetics, or clonidine, the place of morphine as first choice ITA-drug was never really challenged before the apparition of the non-opioid ziconotide, which has now for a decade been considered a first line ITA-drug by the Polyanalgesic Consensus Conference (PACC) (Deer et al., 2007; Deer et al., 2017c; Deer et al., 2012). No ITA-drug has been as thoroughly investigated as ziconotide, including three pivotal randomized controlled trials (RCTs) (Rauck et al., 2006; Staats et al., 2004; Wallace et al., 2006) and many open-label studies in diverse study populations (Alicino et al., 2012; Deer et al., 2017a; Deer et al., 2009; Dupoiron et al., 2012; Ellis et al., 2008; Raffaeli et al., 2011; Saulino et al., 2009; Wallace et al., 2008; Webster et al., 2009; Ver Donck et al., 2008). However, despite algorithms such as the ones published by PACC (Deer et al., 2017c), the optimal use of ziconotide and other ITA drugs in clinical practice is not self-evident. Indeed, it is important to bear in mind that pharmacological treatment is only a small part of the management of chronic non-cancer pain, and that ITA itself in many ways is a last resort when it comes to the pharmacological treatment of chronic non-cancer pain (Turk et al., 2011).

Based on (1) previous knowledge of the literature (as demonstrated by previous work in the field (Bäckryd 2015; Bäckryd et al., 2015)), (2) clinical experience and (3) an updated PubMed search for recent developments (see under Literature Search Methods), the aim of this paper is to provide a

practitioner-oriented, educational, narrative, up-to-date review on the use of ziconotide in clinical pain medicine. Given the fact that the Summary of Product Characteristics (**SPC**) is in part incongruent with the latest dosing recommendations (Deer et al., 2017b; Web Reference 3), such an update seem warranted from a safety point of view.

Literature search methods

In addition to previous knowledge of the literature, a PubMed search using the word "ziconotide" yielded 369 counts (28 December 2017), the yearly distribution being depicted in **Figure 1**. The 5 years limit function was applied to the search, yielding a total of 88 articles whose abstract were screened in order to ensure up-to-dateness concerning recent published clinical data. New pre-clinical papers were not considered relevant to the aim of the present paper.

Is ziconotide really that effective in clinical practice?

Although there is one small study on acute postoperative pain (Atanassoff et al., 2000), it is important to remember that ziconotide is approved for the treatment of chronic pain. The three pivotal RCTs underlying the approval of ziconotide (Rauck et al., 2006; Staats et al., 2004; Wallace et al., 2006) have recently been reviewed in a meta-analysis (Brookes et al., 2017). All three studies defined a responder as a patient experiencing ≥30% reduction of visual analogue scale pain intensity (VASPI) at follow up, and the meta-analysis of (Brookes et al., 2017) yielded a pooled odds ratio (95% confidence interval) of 2.77 (1.37-5.59), hence favouring ziconotide over placebo.

The number needed to treat (NNT), which is the inverse of the absolute risk reduction (Edelsberg and Oster 2009), is an alternative effect size measure (McGough and Faraone 2009). Based on the figures tabulated by (Brookes et al., 2017), the NNT for 30% reduction in VASPI was calculated by the present author to be 5.56. However, it is important to remember that in two of the studies (Rauck et al., 2006; Staats et al., 2004), dosages were much higher than those described in the subsequent **SPC** (Web Reference 3), whereas in (Rauck et al., 2006) (with dosages corresponding to the subsequent **SPC**) the proportion of responders was not significantly different between groups (although statistical significance was noted for VASPI mean percentage improvement from baseline to week 3). Hence, the clinical validity of the effect sizes described above should be critically pondered. This is especially important when considering that recent starting dosage recommendations are more cautious than even the **SPC** (see below) (McDowell and Pope 2016; Web Reference 3). Given the obvious clinical fact that ITA is much more of a last resort than a first-line option in the armamentarium of the pain physician, and given the high NNT for analgesics in general in chronic pain conditions (as exemplified for instance by (Finnerup et al., 2015) for neuropathic pain), it is perhaps no surprise that there are many non-responders. As aptly expressed by Brookes et al. (2017), ziconotide "should not be seen as a panacea".

Although case reports and small case series can give valuable information and should therefore be published (recent examples are the papers by: de la Calle Gil et al., 2015; Heifets et al., 2013; Horazeck et al., 2015; Lanzillo et al., 2016; Lux 2010; Narain et al., 2015; Obafemi and Roth 2013; Patel et al., 2017b; Phan and Waldfogel 2015; Pozzi et al., 2014; Russo et al., 2015; Staquet et al., 2016; Voirin et al., 2016), "real life" data from larger cohorts such as the Registry of Intrathecal Ziconotide

Management (PRIZM) (Deer et al., 2017a) are more valuable. A recent interim analysis of the PRIZM study showed that, after 12 months of treatment, 34.8% of patients on ziconotide experienced ≥30% pain intensity reduction (Deer et al., 2017a). However, and most importantly when it comes to generalizability, only 23 out of 93 enrolled patients reported data at 12 months, the authors stating the following "possible reasons" for this high frequency of missing values: study discontinuation; missed assessment; recently enrolled patients not yet reaching that time point. High frequencies of treatment discontinuation have indeed been observed by other investigators in similar open-label studies (Ellis et al., 2008; Raffaeli et al., 2011; Wallace et al., 2008; Webster et al., 2009). All in all, although the analgesic effect of ziconotide has been demonstrated in RCTs, the magnitude of its long-term effect size in clinical practice is difficult to ascertain. That there is a subset of patients who experience long-term clinically significant relief while on ziconotide is however undeniable.

Is ziconotide safe to use?

Opioid-like adverse effects such as respiratory depression, tolerance, dependency or hormonal changes have not been described for ziconotide (Schmidtko et al., 2010; Webster 2015). However, this obvious advantage is counter-balanced by the fact that ziconotide has a narrow therapeutic window with numerous neurological side effects (see below) as well as a substantial time lag after dose titration (probably because of hydrophilicity-related slow diffusion into neural tissue) (Schmidtko et al., 2010). Hence, the adage "start low, go slow" is important to bear in mind for this drug (Brookes et al., 2017), and the present writer routinely follows the advice of *not* augmenting the dose more often than once a week (Fisher et al., 2005). Dosing issues are addressed in more detail below.

According to the **SPC**, the most common adverse reactions reported in clinical trials were dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), gait abnormal (16%), memory impairment (13%), blurred vision (14%), headache (12%), asthenia (13%), vomiting (11%), and somnolence (10%); most adverse reactions were mild to moderate in severity and resolved over time (Web Reference 3). Due to the fact that the RCTs used much higher dosages than are nowadays recommended (see below), it is also of great interest to ponder registry open-label reports of side-effects such as those from the Italian registry of ziconotide with mean doses after 6 months ranging from 3.2 to 5.1 mcg/day depending on diagnosis; these data are summarized in **Figure 2**.

Of the numerous neurological side effects that have been described, the most feared are the neuropsychiatric ones, which are thought to be associated with rapid titration and high dosages (Sanford 2013). Suicidality, psychosis and confusion are of particular concern (Maier et al., 2011; Phan and Waldfogel 2015; Webster 2015). Hence, on the (unproven but sensible) assumption that a patient's prior psychiatric disorders may be a predisposition for dangerous neuropsychiatric adverse effects, the patient's psychological state should be carefully evaluated before considering ziconotide treatment (Deer et al., 2012). At the very least, a history of psychosis should be seen as a contraindication (Brookes et al., 2017; Deer et al., 2012). Low-dose strategies have substantially mitigated, but not eliminated, the risk of serious neuropsychiatric side effects (Deer et al., 2012). If a severe adverse reaction occurs, ziconotide infusion should and can be stopped immediately without withdrawal effects (Kress et al., 2009).

Weighing potential benefits against risks

Bearing in mind both the shown efficacy of intrathecal ziconotide infusion in short RCTs *and* its potential neuropsychiatric dangers, pain practitioners must balance the one against the other in their "tailor-made" handling of the individual patient (**Figure 3**). In the decision-making process, the following factors should at least be weighed in.

Patient selection

Although it is probably true that ITA should no longer been seen exclusively as a last resort salvage therapy (Deer et al., 2017c), it is nevertheless still the case that it is only suitable for a minority of chronic pain patients. This being a review of the use of ziconotide in particular and not on the use of ITA in general, the following will focus on the particulars of ziconotide. If ITA is indeed indicated, which patients should be treated with ziconotide, as opposed to other ITA-drugs?

Cancer pain

The latest PACC recommendations (Deer et al., 2017c) emphasize that cancer stage and life expectancy should be taken into consideration when selecting ITA medication for cancer pain, and the following three categories of cancer patients are defined:

- Category 1: Patient with imminent death or with relatively short life expectancy
- Category 2: Stable or slowed disease, with high likelihood of recurrence or progression
- Category 3: Cancer in partial remission or cured, with residual chronic pain

Although monotherapy with ziconotide or morphine has the strongest evidence base, the PACC recommendations recognize that titratability is of paramount importance for Categories 1 and 2, and that there is significant evidence for using an opioid ± bupivacaine in this population. Confirming this assertion, and from a European perspective, there are several case series reporting the use of an external pump connected to an externalized intrathecal catheter or to a subcutaneous port (i.e., a much less invasive procedure than implanting a pump) (Bäckryd and Larsson 2011; Dahm et al., 2000; Mercadante et al., 2007; Nitescu et al., 1995; Sjoberg et al., 1991; Sjoberg et al., 1994). In advanced cancer and/or in the end-of-life setting, the slowness of titration inherent in ziconotide treatment seems to be a clear drawback compared to opioids and local anesthetics such as bupivacaine. All in all, it is especially important to individualize the ITA treatment for Categories 1 and 2, i.e., to base the treatment on disease progression and in collaboration with the oncology team (Bruel and Burton 2016).

Non-cancer pain

For Category 3 patients (i.e., including "cancer survivors") and for patients with non-cancer pain, monotherapy with ziconotide or morphine are first line options (Deer et al., 2017c). However, the PACC panel stated as a consensus point that "unless contraindicated, ziconotide should be the first drug selected in the population of noncancer patients discussed in this consensus" (Deer et al., 2017c). This is true whether the pain is nociceptive or neuropathic. However, it has to be remembered that in the two non-cancer RCTs (Rauck et al., 2006; Wallace et al., 2006), about 75% of the patients had a neuropathic pain condition.

The latest PACC offer detailed recommendations and multiple algorithms and tables (Deer et al., 2017c). In **Figure 4**, an overview algorithm is proposed, synthesizing the above-given information in

the simplest possible manner. Needless to say, **Figure 4** is no substitute for the PACC or other more in-depths documents.

Trialing procedures

As part of the clinical decision-making process, pre-implantation trialing with the planned analgesic seems rational (Deer et al., 2017b). For ziconotide, this may be done either by using an external pump for a limited period (perhaps 1-4 weeks), or by a bolus injection (Burton et al., 2010). Bolus injection is much simpler, and seems to have become the preferred trialing technique (Deer et al., 2017b). However, because of surprisingly low rates of analgesic effect in an open-label bolus study, the rationale of trialing ziconotide by bolus injection has been questioned (Bäckryd et al., 2015). There are, however, open-label studies that report good analgesia by bolus injections (Mohammed et al., 2013; Pope and Deer 2015). This discrepancy is difficult to explain. The majority view seems to be that bolus injection is a valuable method, but whether this is right or not is arguably a matter for debate. Trialing by external pump infusion has been shown to be feasible (Ver Donck et al., 2008), and this method gives the patient more time to assess efficacy. A case report on the external pump trialing method is presented in **Figure 5**. At the very least, a pain diary should be part of the evaluation.

Studies have shown that there is limited rostral spread of ITA-drugs within the IT space, and there is therefore nowadays a consensus (despite no hard evidence) that catheter tip placement congruent with the dermatomal area of pain is important (Deer et al., 2017c).

Dosing issues

As per the **SPC**, the start dose is 2.4 µg/day (Web Reference 3). If 1-2 weeks of infusion at that dose does not give ≥30% pain reduction, the present writer considers the trial to be negative and a permanent pump will therefore *not* be implanted. Such strict trialing generates a number of negative trialing issues, but given the potential neuropsychiatric side effects of ziconotide (which appear in large part to be dose-related (Sanford 2013)), there is arguably a lot to commend for such a cautious *primum non nocere* approach. It is also important to note that 2.4 µg/day is at the *upper* end of what is nowadays recommended as start dosage (i.e., 0.5-2.4 µg/day) (Deer et al., 2017b).

In case of emergency, a ziconotide infusion can be stopped immediately without withdrawal effects (Kress et al., 2009). Based on the above-mentioned CSF half-life time (median 4.5 hours), ziconotide should be practically cleared from CSF 24 hours after treatment interruption (i.e. after approximately 5 half-lives). However, the resolution of adverse effects takes much more time, i.e., there is a time lag between CSF pharmacokinetics and the pharmacodynamics of ziconotide (Pope et al., 2017; Smith and Deer 2009).

The median time to onset of the most commonly reported adverse events has ranged from 3 to 9.5 days (Smith and Deer 2009). Hence, increasing doses no more often than at least once a week makes sense (Fisher et al., 2005); however, this is much slower than what the **SPC** allows (Web Reference 3). Concerning the magnitude of dose increments, dose increments of up to 1.2 µg/day seem safe, and this low-dose practice is consistent with the recent publication from Prusik et al (2017).

The maximum dosage as per the **SPC** is 21.6 µg/day; however, the **SPC** also states that "approximately 75% of patients who respond satisfactorily to treatment require a dose ≤9.6 µg/day (Web Reference 3). If a strict trailing strategy is followed as described above, high doses should rarely be needed.

Whether the novel nocturnal flex bolus dosing described by Pope and Deer (2015) is advantageous or not will have to be shown in future studies.

Psychiatric evaluation before and during treatment

Before initiating ziconotide treatment, the patient's psychological state should be carefully evaluated. There is an (unproven but sensible) assumption that a patient's prior psychiatric disorders may be a predisposition for dangerous neuropsychiatric adverse effects (Deer et al., 2012). At the very least, a history of psychosis should be seen as a contraindication (Brookes et al., 2017; Deer et al., 2012).

Continual psychiatric review is mandatory when a patient is on ziconotide, and both patients and relatives should be educated in this regard. Psychotic features and suicidal thoughts should be especially sought for.

Conclusion

The current US "opioid epidemic" and its catastrophic consequences, as well as the weak evidence base for the use of opioids in chronic pain conditions, illustrates how difficult it is to "hijack" the endogenous opioid system without creating harm (Ballantyne and Sullivan 2017; Clauw 2017). How to use opioids is a problem facing every pain physician, and the European Pain Federation has recently published a position paper on the appropriate use of opioids in chronic pain (O'Brien et al., 2017). In this context, some researchers have described cannabis-based drugs as a possible alternative, e.g. for "harm reduction" (Lau et al., 2015). Concerning cannabis-based analgesia *per se*, an overview of systematic review has recently been published (Hauser et al., 2017), and there seems to be a gap between public belief and available medical evidence (Fitzcharles et al., 2014).

But does the future perhaps belong not to opium-based or even cannabis-based analgesics but to venom-based drugs? If the age of indiscriminate use of opium-based analgesics is passing, has the age of venom-based products begun? Only time will tell. For the time being, there is but one animal toxin based analgesic on the market and, with all its drawbacks, ziconotide is nonetheless an important part of the armamentarium of modern interventional pain medicine. If ITA is deemed necessary, ziconotide is a rational alternative, at least in chronic (neuropathic) non-cancer pain. However, in many European countries (e.g., the Nordic countries or the UK (Brookes et al., 2017)), ziconotide treatment is only available in a few centers.

Will future pain physician look back on ziconotide as the prototypical example of a new era of venom-based analgesics? Perhaps, but this will presuppose new and easier administration routes, e.g. using "nanocontainers" (Anand et al., 2015; Manda et al., 2016). All in all, the psychiatric side effects of opioids, cannabinoids and ziconotide are a sobering reminder of how difficult it is to interfere safely with receptors in the central nervous system. In that respect, the safety profile of ziconotide is not fundamentally more worrying that that of opioids or cannabinoids; it is just different.

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Legend to the Figures

Figure 1: Yearly PubMed counts for the search word "ziconotide" 1992-2017

Figure 2: Ziconotide-related adverse events recorded in the Italian registry of ziconotide. Based on tabulated data in (Raffaeli et al., 2011)

Figure 3: Balancing potential benefits and risks when considering intrathecal ziconotide

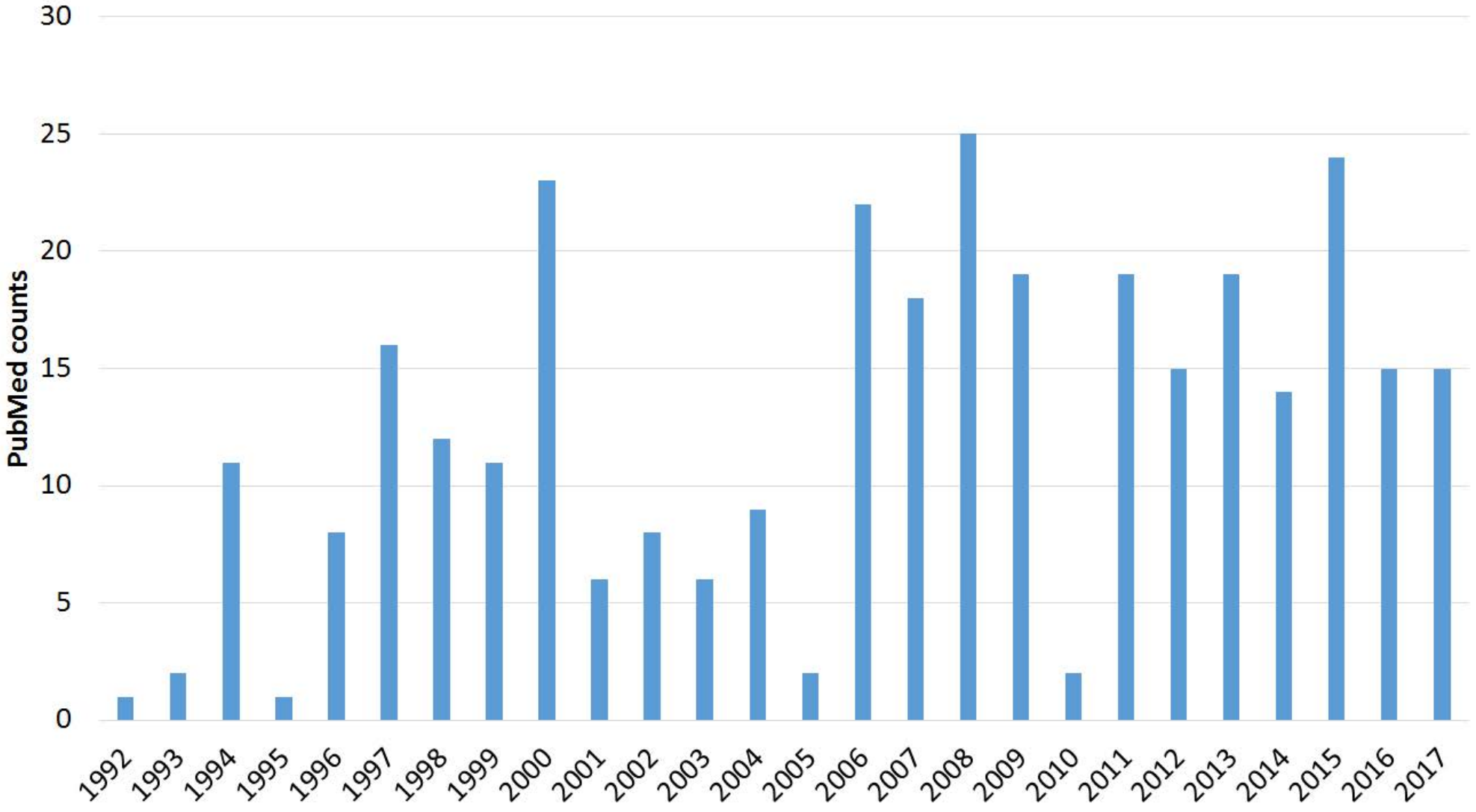
RCT=Randomized Controlled Trial.

Figure 4: Overall decision-making algorithm focusing on ziconotide

ITA = Intrathecal Analgesia; PACC = Polyanalgesic Consensus Conference (Deer et al., 2017c)

Figure 5: Case report of successful ziconotide trialing with external pump

Notes for panel (d): BPI=Brief Pain Inventory. Colour codes: Blue, general activity. Green, mood. Grey, normal work. Violet, relations. Yellow, sleep. Red, enjoyment of life.


PubMed counts
30
25
20
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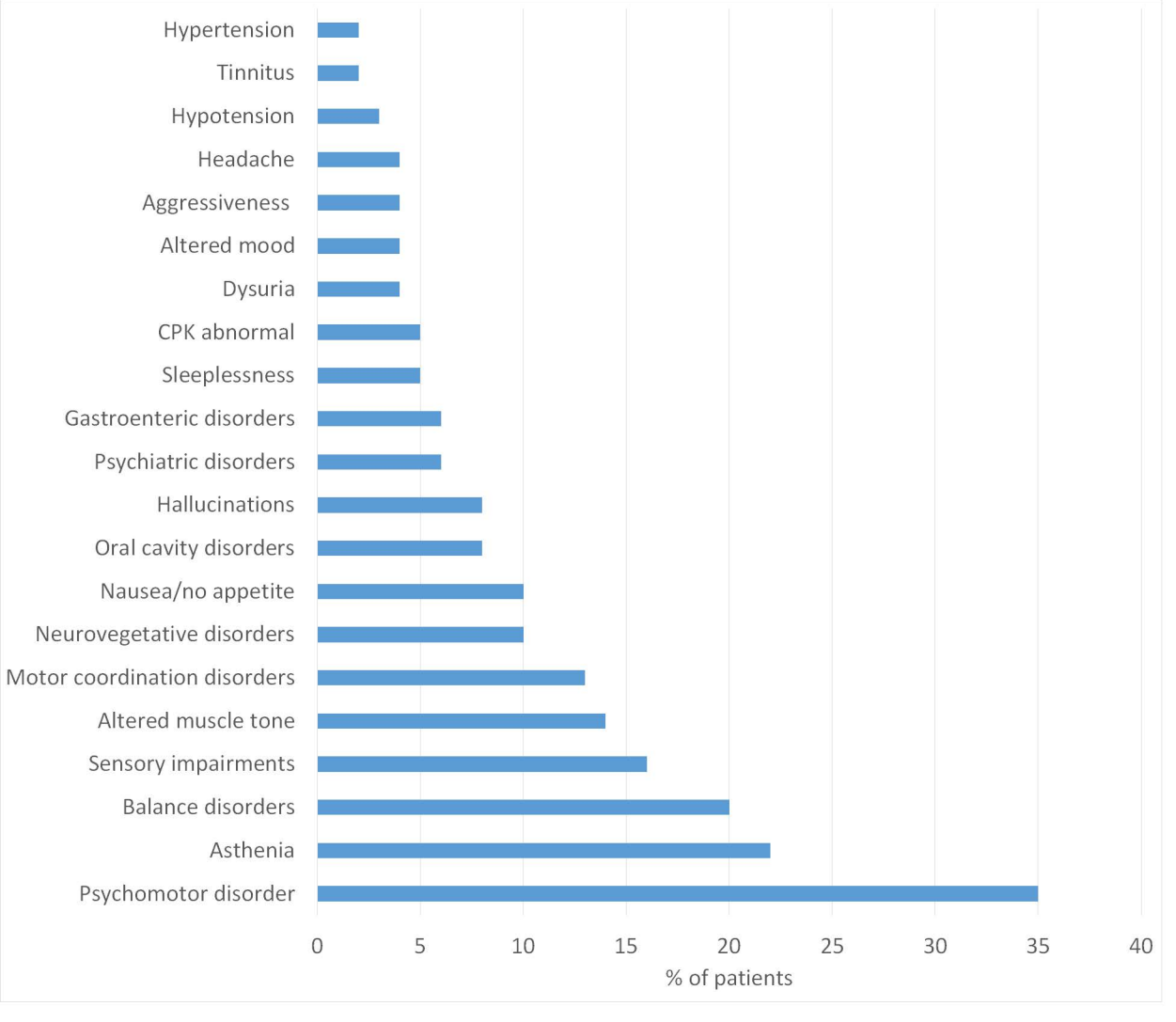
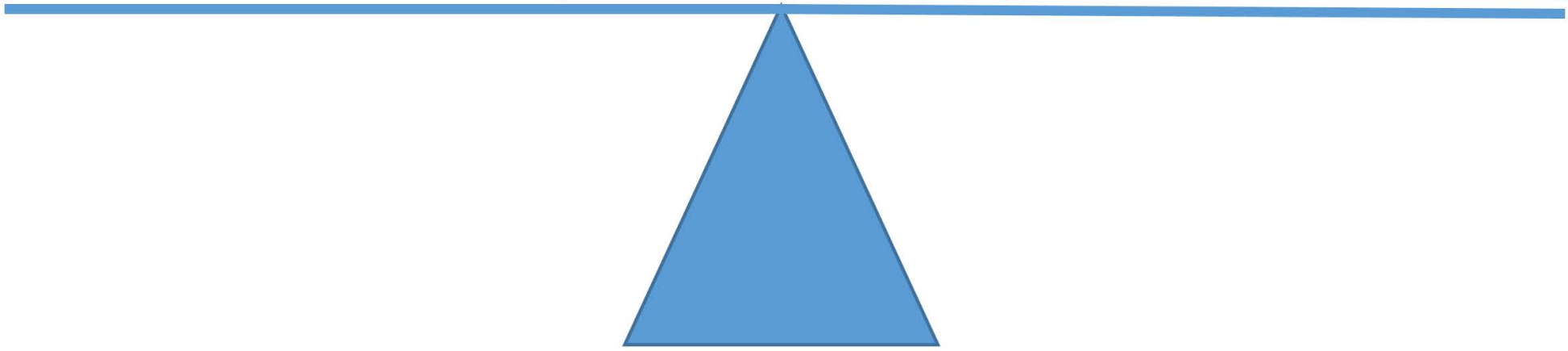
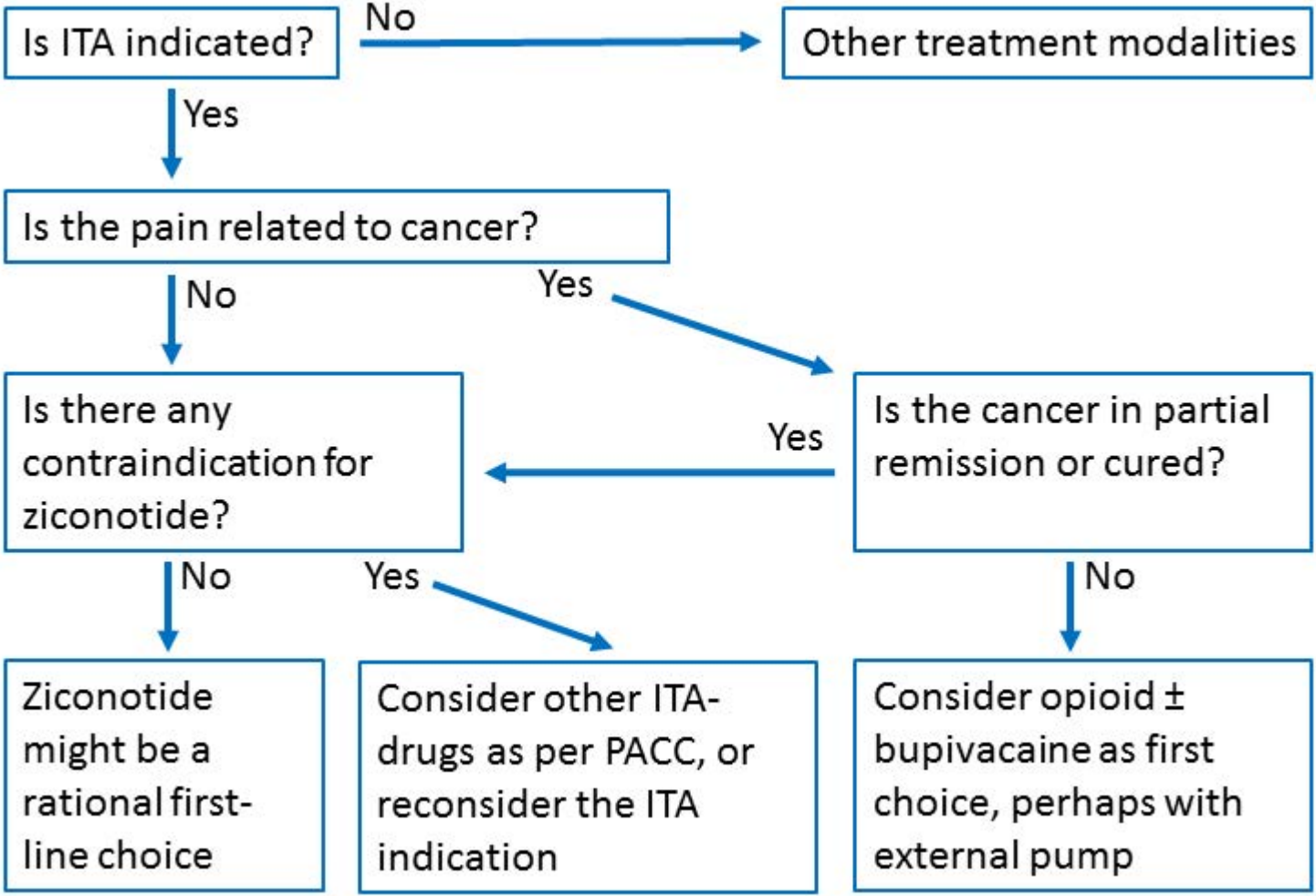

Hypertension
Tinnitus
Hypotension
Headache
Aggressiveness
Altered mood
Dysuria
CPK abnormal
Sleeplessness
Gastroenteric disorders
Psychiatric disorders
Hallucinations
Oral cavity disorders
Nausea/no appetite
Neurovegetative disorders
Motor coordination disorders
Altered muscle tone
Sensory impairments
Balance disorders
Asthenia
Psychomotor disorder
0
5
10
15
20
25
30
35
40
% of patients

Proved efficacy in short RCTs – but what is the long-term effect size?

Neuropsychiatric dangers – but no typical opioid adverse effects




Is ITA indicated?
No
Other treatment modalities
Yes
Is the pain related to cancer?
No
Yes
Is there any contraindication for ziconotide?
Yes
Is the cancer in partial remission or cured?
No
Yes
No
Ziconotide might be a rational first-line choice
Consider other ITA-drugs as per PACC, or reconsider the ITA indication
Consider opioid ± bupivacaine as first choice, perhaps with external pump

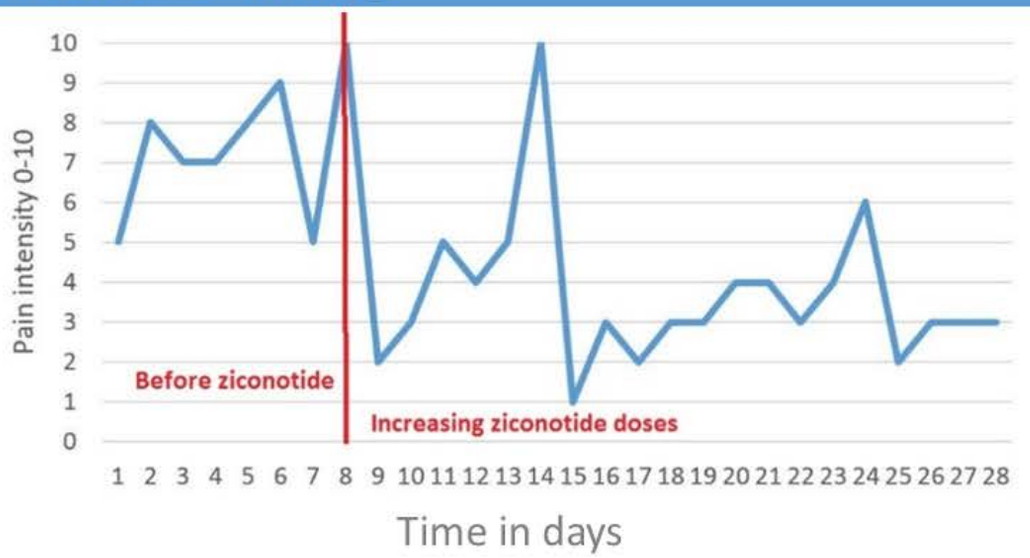
(a) Short case background:

- Middle-aged man
- Trauma and T12 fracture
- Paraparesis
- Severe chronic neuropathic pain left leg
- Refractory to conventional treatment, including tricyclics, gabapentinoids, opioids

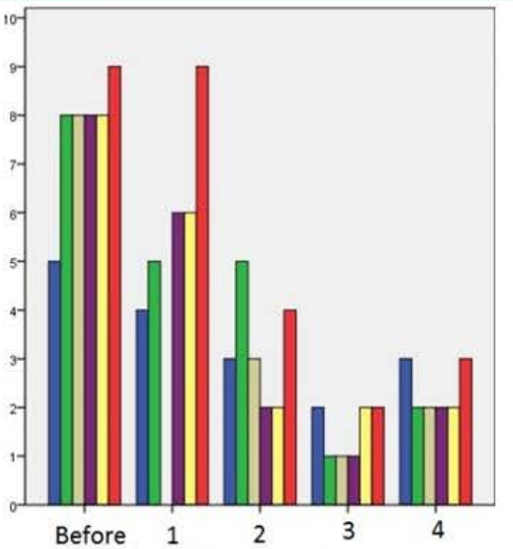
(b) Trialing procedure:

- Intrathecal catheter lumbar level
- External pump
- Ziconotide infusion for 4 weeks, starting with 1.2 µg/day, increasing slowly to 3.6 µg/day
- Clinical effect of trial described in panels (c) and (d)

(c) Daily pain intensity (0-10) before and during ziconotide trialing



(d) Interference items of the BPI (0-10) week 0-4



(e) Evaluation 5 years after pump implantation:

- Patient global impression of change: ”Before ziconotide, I couldn’t handle it, now it’s manageable”
- Dosage of ziconotide 4.2 microg/day; no side-effects; refill every 2-3 months; still on pregabalin; occasional oxycodone PRN