

## Intrathecal Drug Delivery for Neuropathic Pain

David E Jamison, MD,<sup>1</sup> Indy M Wilkinson, MD<sup>2</sup> and Steven P Cohen, MD<sup>3</sup>

1. Assistant Professor, Uniformed Services University of the Health Sciences and Walter Reed National Military Medical Center; 2. Resident in Anesthesiology, National Capital Consortium; 3. Professor of Anesthesiology, Uniformed Services University of the Health Sciences, and Associate Professor, Johns Hopkins School of Medicine

### Abstract

Neuropathic pain represents a substantial burden on society. The treatment of neuropathic pain is challenging and typically involves multiple medication classes such as anticonvulsants, antidepressants, and opioids. The advent of intrathecal medication delivery in the late 1970s provided an additional option for the treatment of refractory neuropathic pain. This article presents a review of the evidence regarding intrathecal medications for neuropathic pain. There is strong evidence to support the use of intrathecal opioids in malignant pain of mixed characteristics, and moderate evidence for their use in non-malignant, neuropathic pain. The use of baclofen is strongly supported for spasticity, but there is only intermediate-level evidence for its use in neuropathic pain. With respect to clonidine and ziconotide, there is moderate evidence to support their use for neuropathic pain, although the effectiveness of the latter agent is limited by the high incidence of adverse effects. For steroids, there is weak evidence in favor of its use in neuropathic pain, predominantly in combination with opioids. The evidence is moderate to strong for the use of steroids in post-herpetic neuralgia, which must be weighed against the possibility of neurotoxicity if depot steroids are injected.

### Keywords

Intrathecal, neuropathic pain, spinal analgesia, ziconotide, baclofen, morphine, clonidine, methylprednisolone, post-herpetic neuralgia, failed back surgery syndrome

**Disclosure:** The authors have no conflicts of interest to declare.

**Acknowledgment:** The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

**Received:** October 28, 2011 **Accepted:** November 7, 2011 **Citation:** *US Neurology*, 2011;7(2):154–62 DOI: 10.17925/USN.2011.07.02.154

**Correspondence:** Steven P Cohen, MD, 550 North Broadway, Suite 301, Baltimore, MD 21029. E: scohen40@jhmi.edu

Neuropathic pain may arise from a variety of causes involving either the central or peripheral nervous system, and is typically challenging to treat. The annual incidence of neuropathic pain is estimated to be 1 %, with the burden likely to increase as the population ages.<sup>1</sup> When traditional mainstays of treatment fail to provide relief, more advanced interventions such as neuromodulation and intrathecal therapy may result in symptom palliation.

The practice of introducing medication into the intrathecal space can be traced to the accidental spinal anesthetic performed by the neurologist J Leonard Corning in 1885.<sup>2</sup> Corning's intention was to inject cocaine solution onto a dog's lumbar nerve roots, but the needle inadvertently pierced the dura with resultant lower-extremity paresis. He subsequently applied this technique in the treatment of neurologic disorders in humans. The first use of spinal anesthesia was in 1899 by Augustus Bier after he and his assistant took turns performing spinals on each other.<sup>3</sup> Shortly thereafter, Bier reported a series of six lower-extremity surgeries performed under spinal anesthesia.<sup>4</sup>

The discovery of opioid receptors in the central nervous system in the early 1970s led to the proposal that medications could be introduced into

the spinal fluid for analgesia as well as anesthesia. This presumption was borne out in animal models and eventually human cancer patients. Early intrathecal analgesia focused on the use of opioids for the treatment of cancer pain, but this soon evolved to include treatment for non-malignant pain and spasticity. In addition to opioids, medications that can be injected into the subarachnoid space to provide analgesia include alpha-2 adrenergic agonists, calcium channel blockers, gamma-aminobutyric acid agonists, local anesthetics, and corticosteroids.

The decision to proceed with intrathecal therapy is based on a number of criteria:

- chronic pain condition refractory to more conservative therapy;
- no medical contraindication to implantation surgery;
- no psychological or sociological contraindication to surgery;
- constant or near-constant pain requiring around-the-clock medication administration;
- no tumor encroachment on the thecal sac;
- life expectancy greater than three months;
- no practical issues that might interfere with pump placement, refill, or maintenance (morbid obesity or cachexia, impending move from

- area, severe cognitive impairment); and
- positive response to an intrathecal trial.

Given that delivery of medications into the subarachnoid space carries risks beyond those associated with the actual medications, the decision to proceed with this therapy must be carefully undertaken. Procedural risks range from the mild, such as post-dural puncture headache, to the potentially catastrophic, such as neuraxial infection or hematoma. Adverse effects attributable to the medications are class-dependent but can be severe, including respiratory depression, seizures, weakness, hallucination, or suicidal ideation. The risks of both the procedure and medication(s) to be delivered must be considered and balanced against the risks of a patient's current therapy and untreated pain.

Selection criteria are intended to identify patients who have failed more conservative therapy and do not have contraindications to intrathecal therapy. In contrast to cancer pain, intrathecal treatment for neuropathic pain poses additional challenges given the variety of etiologies. The primary methods of performing an intrathecal trial are single-shot subarachnoid injection or longer-term trial infusions into either the epidural or subarachnoid space. The trial period is crucial in establishing the efficacy of the proposed therapy and in determining whether adverse effects will be of such prominence as to render the therapy unfeasible. However, an inherent shortcoming is that the development of some adverse effects in the long term may not be predicted by the success of a short-term trial (i.e. tolerance, edema, and hyperalgesia with opioid therapy). Despite the potential risks of intrathecal therapy, in the proper setting it can play an important role in the amelioration of refractory neuropathic pain.

## Opioids

The discovery of opioid receptors in the central nervous system was reported in several studies in 1973.<sup>5-7</sup> This discovery led to experimentation with intrathecal morphine in animals and, ultimately, the first reported use of intrathecal opioids by Wang and colleagues in 1979.<sup>8,9</sup> Following the success noted in Wang's study (all eight patients with refractory cancer-related pain noted resolution of pain with intrathecal morphine), the use of intrathecal opioids in treating a variety of pain conditions has blossomed.

Found in high concentrations in the dorsal horns of the spinal cord, opioid receptors are broadly classified into several subtypes to include mu, delta, and kappa.<sup>10</sup> The mu receptor is the most clinically relevant as it mediates the analgesic effects of commonly used agonists such as morphine, hydromorphone, and fentanyl. Pre-synaptic binding of opioid agonists leads to decreased release of pro-nociceptive neurotransmitters (substance P and calcitonin gene-related peptide), while post-synaptic binding yields increased threshold to action potential via neuronal hyperpolarization.<sup>11</sup>

The clinical effects of intrathecal opioids are dependent not only on their affinity for the opioid receptor but also on their movement and solubility within the cerebrospinal fluid. Among opioids suitable for intrathecal administration, morphine is the most hydrophilic, followed by hydromorphone. Higher levels of hydrophilicity allow greater and faster rostral spread within the cerebrospinal fluid and delay systemic spread. Conversely, the lipophilic characteristics of fentanyl and sufentanil result

in greater systemic absorption and decreased movement within the spinal column. These properties must be taken into account when selecting an agent, as lipophilic agents need to be delivered more proximally to the targeted area than their hydrophilic counterparts.<sup>12</sup>

The first clinical trial researching the effects of intrathecal opioids on chronic pain was published by Smith et al.<sup>13</sup> in 2002. A total of 202 patients with refractory cancer pain were randomized to receive either intrathecal opioids via an implantable drug delivery system (IDDS) plus comprehensive medical management (CMM) or CMM alone. The majority of patients had mixed neuropathic pain (60 % in the CMM group, 61 % in the IDDS group), while an additional 14 % of the CMM group and 13 % of the IDDS group had strictly neuropathic pain. Fifty-one IDDS patients had intrathecal pumps placed within four weeks of their trial. Forty-eight patients had morphine added in their pumps while three received dilaudid; in addition, 15 had bupivacaine, two clonidine, and one droperidol added. At four-week follow-up, the results favored the IDDS group, who displayed an overall greater reduction in visual analog scale (52 versus 39 %) and greater reduction in toxicity-related adverse effects (50 versus 17 %). These results persisted at six-month follow-up. A slight trend was noted whereby the IDDS group displayed greater survival at six months (54 versus 37 %). Rauck and colleagues<sup>14</sup> published a multicenter, prospective, open-label study investigating the effects of intrathecal morphine in cancer patients in 2003. Among the 124 enrolled patients with refractory cancer pain, 119 went on to have a successful trial and were implanted with an IDDS. The study did not detail the nature of the patients' pain characteristics, although it is reasonable to assume there were high rates of neuropathic pain. A 31 % reduction in pain score at one month post-implantation was observed, which was maintained until the final follow-up at 16 months. The data also demonstrated a statistically significant decrease in systemic opioid-related adverse effects.

There are several large retrospective studies which have shown good effect for intrathecal opioids in malignant and non-malignant pain. A 1996 retrospective, multicenter study performed by Paice et al.<sup>15</sup> collected data on 429 patients receiving intrathecal opioids via an IDDS. The study consisted of a survey sent to physicians and patients for the purpose of collecting data on screening, outcomes, dosing, and adverse effects. Commensurate with prior and subsequent studies, there was a strong presence of neuropathic pain among the patient population (38 % with purely neuropathic pain, with an equal proportion suffering from mixed somatic and neuropathic pain). Overall, patients reported a mean pain reduction of 61 % following initiation of therapy. Two-thirds reported they were very satisfied with their pain relief, 20 % reported moderate satisfaction, and only 4 % reported being very dissatisfied. Winkelmüller and Winkelmüller<sup>16</sup> conducted a similar study in 1996 examining the results of 120 patients with primarily neuropathic pain. The results showed a mean pain reduction of 67 % six months following initiation of intrathecal opioid therapy and a mean reduction of 58 % at the longest follow-up of four years. Similar rates of pain relief and patient satisfaction have been attained in other retrospective studies of patients with neuropathic and mixed somatic-neuropathic pain conditions.<sup>17-19</sup>

Although randomized and prospective trials have not been performed to address the role of intrathecal opioids in strictly neuropathic pain conditions, the overall evidence is good given the high prevalence of

**Table 1: Conversion Ratios Between Routes of Administration for Commonly Used Opioids and Baclofen**

Agent	Oral (mg)	Parenteral (mg)	Epidural (mg)	Intrathecal (mg)	Hydrophilicity
Morphine	300	100	10	1	High
Hydromorphone	40–60	10	2	0.2	Intermediate
Meperidine	3,000	1,000	100	10	Low
Fentanyl	–	1	0.1	0.01	Low
Sufentanil	–	0.1	0.01	0.001	Low
Baclofen	1	–	–	0.005	High

Note: ratios between opioids and baclofen do not represent equianalgesic doses.

neuropathic and mixed pain characteristics in available studies. There are several retrospective studies of small size documenting the potential benefits of intrathecal opioids in complex regional pain syndrome (CRPS),<sup>20,21</sup> but randomized prospective studies are lacking.

A major advantage of intrathecal administration of opioids lies in the low equianalgesic dose compared with oral opioids (roughly 300:1 for both morphine and hydromorphone). While this tends to result in fewer opioid-related systemic adverse effects, prospective studies have noted common adverse effects to include sedation, constipation, confusion, and hypogonadism. Complications related to pumps and their surgical implantation (e.g. catheter migration and kinking, infection, need for surgical revision) have been reported to occur in between 6 and 25 % of patients.<sup>13,14,22</sup> Catheter tip granuloma formation is a serious and potentially devastating complication and a controversial topic. Animal studies suggest that granuloma formation is directly correlated to increasing opioid dose and concentration, although a recent retrospective study in humans refutes this.<sup>23,24</sup> It has been suggested that concomitant administration of intrathecal clonidine is protective against granuloma formation, although the evidence for this is weak and the possible mechanism for this purported protection remains unclear.<sup>24,25</sup> Table 1 summarizes the conversion ratios between routes of administration for commonly used opioids and baclofen.

### Gamma-aminobutyric Acid Agonists

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter widely distributed throughout the nervous system. Activation of GABA receptor subtypes GABA-A and GABA-B results in an intracellular influx of chloride ions, hyperpolarizing the neural cell membrane and decreasing excitability. The GABA-A receptor exists as a ligand-gated (ionotropic) chloride channel, whereas the GABA-B receptor is a G-protein-linked (metabotropic) complex whose activation results in amplification of current through potassium channels. GABA-B receptors are found both pre- and post-synaptically. Pre-synaptic activation results in decreased excitatory neurotransmitter release, while post-synaptic activation leads to membrane hyperpolarization.<sup>26</sup> Although some literature refers to a third receptor (GABAC), the close relation of this receptor to GABA-A in sequence, structure, and function has caused the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology to recommend that these receptors be referred to as part of a sub-family of GABA-A.<sup>27</sup>

Common GABA-A receptor agonists include ethanol, barbiturates, benzodiazepines, zolpidem, and eszopiclone, but only midazolam

has been shown to be efficacious in treating neuropathic pain when administered intrathecally. Midazolam is currently a fourth-line intrathecal treatment for chronic pain.<sup>28</sup> Spinal GABA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have been implicated in the mechanisms of neuropathic pain after nerve injury. Using a rat model, Lim et al.<sup>29</sup> demonstrated that spinal GABA-A receptor activation by intrathecal midazolam attenuated the expression and function of spinal AMPA receptors in rats following peripheral nerve injury, ultimately reducing thermal hyperalgesia and mechanical allodynia compared with a control group.

In a randomized trial, Dureja et al.<sup>30</sup> studied the effects of 2 mg intrathecal midazolam with and without epidural methylprednisolone when administered to patients suffering from lumbosacral post-herpetic neuralgia. Not only did the group receiving intrathecal midazolam monotherapy report lower pain scores and allodynia for up to 12 weeks post-injection, the combination was found to behave synergistically. In another clinical trial, Borg and Krijnen<sup>31</sup> treated four patients with chronic benign neurogenic and musculoskeletal pain refractory to conventional analgesics with continuous infusions of up to 6 mg/day of intrathecal midazolam in combination with clonidine or morphine. In all four patients, long-term infusion therapy resulted in nearly complete abolishment of pain symptoms.

Inasmuch as dorsal horn GABA receptor inhibition has been demonstrated to play an important role in neuropathic pain following nerve injury,<sup>32</sup> elucidation of the inhibitory mechanisms has led researchers to postulate that the addition of acetazolamide and its inhibition of carbonic anhydrase would enhance the efficacy of GABAergic inhibition in the context of neuropathic pain. Asiedu et al.<sup>33</sup> found that spinal co-administration of acetazolamide and midazolam acts synergistically to reduce neuropathic allodynia after peripheral nerve injury.

Animal studies assessing the toxicity of intrathecal midazolam have yielded conflicting results, with approximately half reporting neurotoxicity.<sup>34</sup> Deleterious effects have been observed with as little as a single dose, but many studies have shown no pathologic effects after continuous usage, prompting some to conclude that intrathecal midazolam is no more neurotoxic than normal saline.<sup>35,36</sup> In a cohort study evaluating the effects of adding 2 mg of midazolam to local anesthetic in 1,100 patients undergoing spinal anesthesia, Tucker et al.<sup>37</sup> found no increase in post-operative neurologic symptoms over local anesthetic alone.

Fewer GABA-B agonists are commercially available, but baclofen has shown to be efficacious when given intrathecally to treat spasticity, CRPS, and central pain secondary to stroke or spinal cord injury (SCI). Whereas intrathecal baclofen is currently a first-line agent for the treatment of spasticity secondary to SCI, multiple sclerosis, and other disorders, recent studies have been able to distinguish between the analgesic and spasmolytic properties. These effects are not reversed by the opioid antagonist naloxone, suggesting that GABAergic analgesia occurs via a separate pathway not shared by endogenous opiates. Baclofen is currently considered a fourth-line treatment for chronic pain.<sup>28</sup>

In a randomized, double-blind trial, seven women with CRPS were given intrathecal bolus injections of baclofen 25, 50, or 75 µg, or saline.<sup>38</sup> No statistical difference was found between the 25 µg and saline injections,

but higher doses were associated with partial or complete resolution of symptoms. Six of seven women went on to receive implantable baclofen infusion pumps and, at three months post-implant, marked reductions in pain were experienced such that three women had regained normal hand function and the ability to walk. These results were supported by Zuniga and colleagues,<sup>39</sup> who reported two patients with refractory CRPS who experienced dramatic reductions in spontaneous and evoked pain when treated with intrathecal baclofen.

Critics of baclofen analgesia argue that the pain reductions observed are merely the result of elimination of spasm-related pain, but a study conducted by Herman and colleagues<sup>40</sup> demonstrated suppression of neuropathic pain that was temporally distinct from spasm-related pain. In these patients, the suppression and reappearance of dysesthetic pain after a bolus of intrathecal baclofen occurred distinctly from that of spasm-related pain. No difference was noted in evoked pain in these patients. These results were supported by Taira et al.,<sup>41</sup> who found that nine of 14 patients with central pain secondary to stroke or SCI experienced significant reductions in spontaneous pain, allodynia, and hyperalgesia for up to 24 hours following intrathecal baclofen bolus.

In addition to alleviating central pain, intrathecal baclofen has shown efficacy when used to treat neuropathic pain secondary to failed back surgery syndrome (FBSS), amputation, and plexopathy.<sup>42</sup> Lind and colleagues<sup>43</sup> published a case series in which they treated seven patients with refractory neuropathic pain with intrathecal baclofen infusion pumps and spinal cord stimulation, and four with baclofen alone. Both groups obtained significant pain relief, but a greater reduction in pain scores occurred in the combination group. The results were borne out over 67 months of follow-up. These results are further bolstered by a recent placebo-controlled trial conducted in 10 patients experiencing refractory neuropathic pain after spinal cord stimulation (SCS).<sup>44</sup> Clonidine, baclofen, and saline (control) were intrathecally administered by bolus injections in combination with SCS. Seven of 10 patients reported significant pain reduction when SCS was combined with active drugs. The most common adverse effects associated with intrathecal baclofen are somnolence, cognitive impairment, weakness, gastrointestinal complaints, and sexual dysfunction.<sup>45</sup>

### Local Anesthetics

Local anesthetics are sodium-channel-blocking agents that reversibly decrease the rate of depolarization and repolarization in neuromembranes, preventing action potential initiation and inhibiting signal conduction. Local anesthetics block the transmission of all neurons, not just the A-delta and C fibers responsible for the transmission of pain sensation. These agents have been the cornerstone of neuraxial analgesia for surgical pain for decades, but it was not until the 1990s that they were critically evaluated for chronic pain.<sup>46</sup> Few studies to date have sought to isolate local anesthetic efficacy in neuropathic pain.

Most research evaluating intrathecal local anesthetics have used them in conjunction with opioids. Some authors have concluded that the combination provides synergistic effects after the observation that co-administration of bupivacaine diminishes morphine dose progression during long-term intrathecal administration.<sup>47</sup> Bupivacaine, the most commonly studied intrathecal local anesthetic, appears to

be most effective in patients with neuropathic pain.<sup>48</sup> In a prospective cohort trial, Nitescu et al.<sup>49</sup> evaluated bupivacaine in combination with morphine in 90 terminal cancer patients, 81 of whom endorsed either neuropathic or mixed pain. Eighty-six patients (96 %) obtained acceptable (60–100 %) pain relief, and sedative and rescue consumptions were significantly reduced (median follow-up 60 days).

Similar results have been reported with opioid and bupivacaine combinations in non-cancer neuropathic pain. Krames and Lanning<sup>50</sup> found that not only did the addition of bupivacaine enhance analgesia, but its opioid-sparing effects also resulted in decreased adverse effects (mean follow-up 28 months). In a retrospective cohort study conducted in 109 patients with FBSS or metastatic cancer of the spine, Deer et al.<sup>51</sup> found that the combination of opioid and bupivacaine provided superior analgesia, lower (23 %) opioid and adjuvant requirements, and greater patient satisfaction than intrathecal opioids alone. In addition, those who received combination treatment required fewer doctor and emergency room visits.

In therapeutic concentrations, local anesthetics are relatively non-toxic and disrupt neurotransmission in a predictable fashion. The dose escalation of intrathecal local anesthetics is limited by adverse effects. Common adverse effects of intrathecal local anesthetics include numbness, paresthesias, weakness, and bowel/bladder dysfunction. High levels of systemic bupivacaine have been associated with cardiotoxicity, which is difficult to reverse. The incidence of adverse effects can be diminished by using combination therapy with opioids and other agents. In clinical practice, the typical range of intrathecal bupivacaine is less than 35 mg/day.

*Table 2* summarizes the outcomes of prospective studies evaluating intrathecal medications for neuropathic pain.

### Calcium Channel Blockers

Calcium plays a critical role in many intracellular processes, including the transmission of pain. The pro-nociceptive effects of calcium are likely attributable to several factors such as activation of second messenger systems and increased neurotransmitter release. The intracellular movement of calcium is pivotal to these processes and is regulated by several types of voltage-gated ion channels. Among the identified channel subtypes, the N-type voltage-gated calcium channel has been shown in both laboratory and animal models to have the most influence on pain transmission.<sup>52,53</sup> Efforts to ameliorate the response to calcium influx have centered around the intrathecal use of calcium channel blockers and have yielded the newest addition to the intrathecal armamentarium, ziconotide.

Derived from the venom of the predatory marine snail *Conus magnus*, ziconotide became the first calcium channel blocker approved for intrathecal use in 2004. It acts via the selective blockade of the N-type calcium channel, which is concentrated in the superficial layers of the dorsal horns, thereby downregulating the release of pro-nociceptive neurotransmitters.<sup>54</sup> Ziconotide, marketed under the trade name Prialt® (Azur Pharma, Inc., Philadelphia, PA, US), has been shown to be effective in treating a variety of neuropathic pain conditions, including those associated with cancer, FBSS, AIDS, and trigeminal neuralgia.<sup>55</sup>

**Table 2: Outcomes of Prospective Studies Evaluating Intrathecal Medications for Neuropathic Pain**

Study	Medication	Study Type, n	Follow-up (Mean in Years)	Relief of Pain, n %	Condition(s) Studied	Comments and Complications
Kumar et al., 2001 <sup>92</sup>	Morphine, infusion	Prospective, observational, 16	1–4 (mean 1.5)	NO 57, FBSS 61, DA 75	NO, mixed (FBSS), DA	The best long-term results were seen with deafferentation and mixed pain
Anderson and Burchiel, 1999 <sup>93</sup>	Morphine, hydromorphone, infusion	Prospective, observational, 30	2.0	50 % with >25 % pain relief	Mixed (FBSS), NO, DA, NP	Adverse effects managed by dose reduction, addition of bupivacaine, or replacement of morphine with hydromorphone
Angel et al., 1998 <sup>94</sup>	Morphine, infusion	Prospective, observational, 11	0.5–3.0 (mean 2.3)	73	Mixed (FBSS), NP	2 patients experienced bladder dysfunction requiring pump removal
Hassenbusch et al., 1995 <sup>95</sup>	Morphine, sufentanil, infusion	Prospective, comparative, 18	0.8–4.7	61	NP	33 % re-operation rate; edema resolved in 3 patients after switching to sufentanil
Dureja et al., 2010 <sup>90</sup>	Midazolam, bolus with or without epidural methylprednisolone	Prospective, comparative, 150	0.2	60	PHN	Combination therapy with midazolam and epidural methylprednisolone resulted in longer-duration analgesia
Borg and Krijnen, 1996 <sup>31</sup>	Midazolam, bolus	Prospective, observational, 4	0.2–0.5	75–90	NP	Patients studied had pain refractory to conventional analgesics
Van Hilten et al., 2000 <sup>38</sup>	Baclofen, bolus	Prospective, comparative, 7	0.5–3	Functionality studied	CRPS	3 patients regained normal hand function, and 2 of these 3 women regained the ability to walk
Taira et al., 1995 <sup>41</sup>	Baclofen, bolus	Prospective, observational, 9	<0.2	>50	Stroke, SCI	Relief of pain, allodynia, and hyperalgesia appeared 1–2 hours after the injection and persisted for 10–24 hours
Herman et al., 1992 <sup>40</sup>	Baclofen, bolus	Prospective, observational	<0.2	80	MS, SCI, TMy	Temporal dissociation regarding the action on dysesthetic pain and spasticity-related pain
Nitescu et al., 1998 <sup>49</sup>	Bupivacaine with morphine, infusion	Prospective, cohort, 90	0.2	60–100	NP, mixed	Sedative consumption was cut in half
Krames et al., 1993 <sup>50</sup>	Bupivacaine with or without morphine, infusion	Prospective, observational, 16	1–2.5	60–80	NP, NO, mixed	Bupivacaine improved analgesia in 8 of 10 patients with a pure or mixed neuropathic component to their pain
Staats et al., 2004 <sup>56</sup>	Ziconotide, bolus	Prospective, comparative, 111	<0.2	53	NP, AIDS, PHN	25 % increase in incidence of adverse events compared with placebo
Webster et al., 2009 <sup>96</sup>	Ziconotide, infusion	Prospective, observational, 78	3	22–36	NP, NO	Required ziconotide dose remained stable throughout treatment period, suggesting no development of tolerance
Siddall et al., 2000 <sup>70</sup>	Clonidine with or without morphine, bolus	Prospective, comparative, 15	<0.2	17	NP	Clonidine shown to augment intrathecal morphine analgesia
Eisenach et al., 1998 <sup>71</sup>	Clonidine, bolus	Prospective, comparative, 16	<0.2	35	NP	Higher doses demonstrated both better analgesia and more stable hemodynamics

CRPS = complex regional pain syndrome; DA = deafferentation; FBSS = failed back surgery syndrome; MS = multiple sclerosis; NO = nociceptive; NP = neuropathic; PHN = post herpetic neuralgia; SCI = spinal cord injury; TMy = transverse myelitis.

Staats and colleagues<sup>56</sup> conducted a multicenter, double-blind, placebo-controlled study to assess the efficacy of ziconotide in patients with either malignant or AIDS-related pain. One hundred and eleven patients were enrolled and randomized to receive either ziconotide or placebo. Ziconotide dosing and titration were altered during the study from a starting dose of 0.4 µg/hour to less than 0.1 µg/hour to decrease the incidence of adverse effects; the maximum dose was maintained at 2.4 µg/hour. Overall, significantly better pain relief was observed with ziconotide than placebo (53.0 versus 17.5 %) over a two-week time course. Serious adverse effects were reported in 30.6 % of the treatment group, with the most common complaints being dizziness, confusion, and urinary retention.

A subsequent study by Rauck et al.<sup>57</sup> was designed to determine whether the prevalence of adverse effects could be decreased by using a lower maximum dose and slower titration schedule. Two hundred and twenty patients with refractory non-malignant pain were randomized to either placebo or ziconotide. The most prevalent diagnosis was FBSS consisting of mixed neuropathic and somatic pain. Ziconotide was started at a dose of 0.1 µg/hour and titration was slowly achieved over a three-week period in increments of 0.05–0.1 µg/hour, to a mean dose of 0.29 µg/hour. The study demonstrated superior pain relief in the treatment group (14.7 versus 7.2 %) with a similar rate of adverse effects between the two groups. A total of 12 % of patients in the treatment group experienced serious adverse effects,



which suggests that a lower starting dose and slower titration are better tolerated.

Long-term data are scarce given the fairly recent introduction of ziconotide. In a retrospective study by Raffaelli et al.<sup>58</sup> conducted in 104 patients who received intrathecal ziconotide for both cancer and non-malignant pain, 54 % reported at least 50 % pain relief. Patients receiving ziconotide for one year obtained stable reductions in pain (mean VAS declined from 8.5 to 5.0), suggesting that tolerance does not prominently develop with prolonged administration. Doses ranged from 0.14 to 0.21 µg/hour, with higher doses associated with increased pain relief. Although there were no reported serious adverse effects, 63 % of patients reported at least one adverse effect, with the most common being psychomotor disorders (e.g. confusion and memory impairment), weakness, and balance impairment.

Intrathecal infusions are increasingly composed of mixed solutions to increase efficacy and minimize adverse effects. To assess the co-administration of ziconotide with other agents, Wallace and colleagues<sup>59</sup> performed a multicenter trial to investigate whether the addition of ziconotide to patients already receiving intrathecal opioids improved their pain relief. Twenty-six patients with refractory chronic non-malignant pain (77 % FBSS) despite intrathecal morphine use had ziconotide added to their infusion. Twenty patients completed the titration phase and 18 proceeded to an extension phase lasting up to 72 weeks. At the end of the study, subjects experienced a 17 % decrease in pain at a mean ziconotide dose of 0.077 µg/hour. All patients reported at least one adverse effect, with confusion, dizziness, and hallucinations being among the most common. However, the enhanced benefit of co-administering opioids and ziconotide must be weighed against the decreased stability of ziconotide when mixed with opioids, which is accelerated at higher concentrations. In addition to the above studies, several case reports have documented good relief for refractory facial pain with intrathecal ziconotide.<sup>60-62</sup> Table 3 summarizes common agent-specific adverse effects.

**Alpha-2 Agonists**

Alpha-2 adrenergic receptors have been shown to play an important role in antinociceptive effects mediated at peripheral, spinal, and brainstem sites. These receptors are concentrated near sites of peripheral nerve injury or inflammation, and their activation reduces inflammation and hypersensitivity to tactile stimuli. Several subtypes of alpha-2 receptors have been identified, but evidence from recent studies suggests that the alpha-2A and alpha-2B receptors are primarily responsible for analgesia and sedation.<sup>63,64</sup> Alpha-2 receptor agonists produce their spinal analgesic effects via inhibitory interactions with pre- and post-synaptic primary afferent nociceptive projections onto secondary neurons in the dorsal horn. Pre-synaptically, the binding of alpha-2 agonists results in the inhibition of neurotransmitter release. Post-synaptically, alpha-2 agonists increase potassium conductance through G-coupled channels, hyperpolarizing the cell.

Several other mechanisms underlying alpha-2 agonist-induced analgesia have been proposed, including activation of spinal cholinergic neurons, which may potentiate their analgesic effects. It has also been postulated that the antinociceptive properties of this class of medication are

**Table 3: Common Agent-specific Adverse Effects**

Opioids <sup>16,92,93</sup>	Ziconotide <sup>56,57,59</sup>	Clonidine <sup>69,70</sup>	Bupivacaine <sup>51,97</sup>	Baclofen <sup>38,98</sup>
Adverse Effect %	Adverse Effect %	Adverse Effect %	Adverse Effect %	Adverse Effect %
Constipation 57	Dizziness 39	Hypotension 53	Transient weakness 17	Sedation 29
Sweating 47	Nystagmus 29	Nausea/vomiting 40	Edema 2	Hypotonia 29
Nausea 42	Confusion 26	Sedation 33		Urinary retention 9
Urinary retention 37	Fever 25	Oxygen desaturation 33		Dysphagia 5
Vomiting 33	Hypotension 24	Dry mouth 20		Hallucinations 5
Insomnia/nightmares 28	Sedation 24			Speech difficulty 3
Impotence 21	Nausea 20			
Confusion 15	Abnormal gait 18			
Pruritis 14	Urinary retention 15			
Edema 7	Headache 12			

enhanced through the inhibition of substance P release,<sup>65</sup> while another recent study suggests that the antihyperalgesic and antiallodynic effects of intrathecal alpha-2 agonists are associated with a significant reduction in spinal N-methyl-D-aspartate receptor phosphorylation.<sup>66</sup>

The most studied and only US Food and Drug Administration-approved alpha-2 agonist for intrathecal use is clonidine. Intrathecal clonidine has been studied extensively in animal models and has been shown to safely alleviate neuropathic pain in a dose-dependent manner.<sup>67</sup> In human subjects, clonidine has been used and studied as both a bolus administration and continuous infusion. While trials have shown promise using epidural clonidine infusion as monotherapy in treating CRPS, intrathecal clonidine infusions are typically combined with a local anesthetic or opioid.<sup>68</sup> Some studies of intrathecal clonidine infusion have yielded mixed results and recommend further study.<sup>69</sup>

Siddall and colleagues<sup>70</sup> conducted a double-blind, placebo-controlled study assessing the efficacy of intrathecal clonidine, alone or combined with morphine, in 15 patients with central pain attributable to SCI. A 17 % reduction in pain was observed in the group receiving intrathecal clonidine monotherapy compared with no change in the saline control group four hours post-administration. The group receiving combination intrathecal clonidine and morphine reported a 37 % reduction in pain scores. Eisenach and colleagues<sup>71</sup> compared the effects of intrathecal versus intravenous (IV) clonidine in normal volunteers in the setting of capsaicin injection, which produces pain, hyperalgesia, and allodynia. The IT but not IV injection of 150 µg clonidine reduced capsaicin-induced pain, pain to heat stimulation, and hyperalgesia. The groups did not differ in hemodynamic or sedative effects.

There is no evidence that intrathecal clonidine is neurotoxic, and it does not cause respiratory depression. The most common adverse effects of clonidine are hypotension, sedation, bradycardia, and nausea. The hypotension associated with clonidine administration may be more pronounced at lower doses, since at higher doses this effect

**Table 4: Dose Ranges and Strength of Evidence for Agents by Diagnosis**

Drug	Typical Dose Range	Strength of Evidence by Diagnosis
Morphine	1–20 mg/day	Strong evidence for cancer pain Moderate evidence for non-malignant pain
Hydromorphone	0.5–10 mg/day	Same as morphine
Fentanyl	0.02–0.3 mg/day	Same as morphine
Midazolam	0.2–6 mg/day	Weak evidence for chronic back pain Anecdotal evidence for neuropathic pain
Baclofen	0.05–0.8 mg/day	Strong evidence for spasticity-related pain Moderate evidence for neuropathic pain Weak evidence for central pain
Bupivacaine	4–30 mg/day	Strong evidence for cancer pain Moderate evidence for non-malignant pain
Ziconotide	5–19 µg/day	Moderate evidence for neuropathic pain
Clonidine	0.03–1 mg/day	Moderate evidence for neuropathic pain Weak evidence for back pain Weak evidence for central pain
Dexmedetomidine	Not approved for human use	Animal model evidence for neuropathic pain
Tizanidine	Not approved for human use	Animal model evidence for neuropathic pain

is antagonized by direct peripheral vasoconstriction. If a patient is receiving long-term therapy with clonidine, abrupt cessation can result in rebound hypertension.

An alpha-2 agonist with higher receptor affinity than clonidine is dexmedetomidine. An early study evaluating the effects of intrathecal dexmedetomidine on self-mutilation (autotomy), a behavior that may indicate the presence of neuropathic pain, demonstrated that rats injected with dexmedetomidine after unilateral sciatic nerve section autotomized significantly less than those receiving saline or morphine.<sup>72</sup> However, dexmedetomidine was unsuccessful in preventing autotomy when injected prophylactically. In another trial studying the effects of intrathecal dexmedetomidine in rats following spinal nerve ligation, dexmedetomidine dose-dependently decreased spontaneous locomotor activity, a behavior believed to signify allodynia.<sup>73</sup> In humans, intrathecal dexmedetomidine has not been studied for chronic pain, but a double-blind study performed in 60 patients undergoing transurethral resection of the prostate found that the addition of either intrathecal dexmedetomidine or clonidine to bupivacaine shortened the onset of sensory and motor blockade, prolonged the duration of the block, and preserved hemodynamic stability.<sup>74</sup>

Tizanidine is another alpha-2 receptor agonist that has shown positive results in animal models of neuropathic pain. Kawamata et al.<sup>75</sup> compared the effects of intrathecal tizanidine and clonidine in rats following sciatic nerve ligation. Dose-dependent reversal of thermal and mechanical hyperalgesia was observed for both drugs, with the highest dosages (5 µg tizanidine and 3 µg clonidine) producing statistically significant effects. Compared with clonidine, tizanidine was associated with a faster onset of action and fewer adverse effects. Tizanidine can occasionally cause liver damage.<sup>76</sup> Its intrathecal administration has not been studied in humans. *Table 4* summarizes dose ranges and strength of evidence for agents by diagnosis.

## Steroids

Corticosteroids have profound and complex anti-inflammatory properties. They inhibit the release of an array of pro-inflammatory mediators (prostaglandins, leukotrienes, cytokines, tissue necrosis factor alpha, and others) from multiple types of leukocytes.<sup>77,78</sup> Once used routinely for the treatment of back pain and lumbar radiculopathy, intrathecal injection of steroids fell from favor in the mid-1980s following its implication in the development of adhesive arachnoiditis.<sup>79,80</sup> Although the preservative polyethylene glycol was blamed in several studies, the intrathecal administration of steroids was nevertheless largely abandoned in favor of the epidural route.<sup>81</sup> However, intrathecal steroid injections remain an alternative treatment for refractory post-herpetic neuralgia (PHN).

PHN is a painful neuropathic condition that can occur in up to 10 % of patients following an acute outbreak of herpes zoster. After initial exposure, the varicella zoster virus may lay dormant in the dorsal root ganglia and become activated months to years later.<sup>82</sup> The incidence of PHN in the population increases with age and is associated with decreased immune function. A 1995 population-based study by Donahue et al.<sup>83</sup> noted an almost eight-fold increase in the prevalence of PHN when comparing 24–35-year-olds with those over 75 years of age. Several preventive therapies have shown promise when instituted during the acute zoster outbreak, including antiviral medications,<sup>84,85</sup> tricyclic antidepressants,<sup>86</sup> and zoster vaccine.<sup>87</sup> If preventive measures are not instituted or fail, the treatment of PHN can be challenging; it has been estimated that roughly 2 % of patients with PHN will have ongoing pain five years following their initial outbreak.<sup>88</sup> In those in whom conventional therapies, such as membrane stabilizers, antidepressants, opioids, and topical analgesics, fail, intrathecal steroids can be considered.

Kikuchi and colleagues<sup>89</sup> performed a prospective randomized trial comparing intrathecal with epidural methylprednisolone in 25 patients with chronic PHN pain. Patients were treated four times at one-week intervals and were followed for 24 weeks after treatment. Global pain relief was superior at all data points in the intrathecal group, with 12 of 13 patients reporting good to excellent analgesia throughout the study compared with only two of 12 patients in the epidural group. Of the biochemical markers analyzed, the only statistically significant difference was decreased levels of interleukin-8 in the intrathecal group one week post-treatment and at 24 weeks.

In a prospective, randomized, placebo-controlled study by Kotani et al.,<sup>90</sup> 277 subjects with PHN of over one year's duration received intrathecal methylprednisolone plus lidocaine, lidocaine alone, or no intervention. Similar to the Kikuchi study, injections were performed weekly for four weeks. Compared with the lidocaine only and non-intervention groups, those patients treated with methylprednisolone plus lidocaine exhibited significant improvement: 82 of 89 patients receiving intrathecal steroids reported their pain relief as good or excellent at two-year follow-up, compared with only nine of 181 patients in the other two groups.

In order to determine the relative effectiveness of intrathecal midazolam and steroids, Dureja et al. performed a 12-week double-blind study comparing a single injection of midazolam, methylprednisolone, or the combination in 150 patients with PHN. Although all groups significantly improved, the combination group obtained significantly better and

longer-lasting analgesia than the other two groups. For all treatments, the maximum benefit was observed between one and three weeks.<sup>30</sup>

The potential risk of adhesive arachnoiditis must be taken into account when opting to pursue intrathecal steroid administration. Preservative-free methylprednisolone formulations are not commercially available, but a recent report by Candido et al. described a technique by which they were able to decrease the amount of polyethylene glycol extracted from vials of steroid by an average of 85 % without decreasing the amount of steroid withdrawn.<sup>91</sup> However, as the precise causative agent remains unclear, it is prudent to reserve this treatment for those who have failed safer and more conventional treatments, and to limit the number of intrathecal injections to four.

## Conclusions

Since its introduction more than 30 years ago, the use of intrathecal therapy to provide analgesia has grown steadily. Significant advances have been made with regard to delivery systems, selection criteria,

and the discovery of new drugs that act via non-opioid receptor sites. Opioids remain the most commonly used intrathecal analgesics, and the evidence supporting their use in cancer-related pain remains strong. For neuropathic pain, intrathecal opioids may provide long-term benefit in carefully selected individuals, but this must be weighed against the cumulative risks of long-term intrathecal opioid therapy, including hyperalgesia and endocrine dysfunction. There is very strong evidence to support the use of baclofen as a treatment for spasticity-related pain, and moderate evidence to support its use for neuropathic pain. Although limited by its narrow therapeutic index and high cost, there is good evidence that ziconotide is effective for neuropathic pain. Bupivacaine has a long history of safe use as a spinal analgesic and may provide significant benefit to individuals as an adjunct agent. Because of its opioid-sparing properties and ability to attenuate the sympathetic response, clonidine may be especially useful in patients with neuropathic pain. Future studies should focus on cost-effectiveness, better identification of phenotypes that may respond to intrathecal treatment, and methods to reduce adverse effects and complications. ■

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