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Intrathecal Drug Delivery

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Intrathecal analgesia has emerged as a key therapeutic option for pain relief for patients who have failed other treatment avenues as well as patients with adequate analgesia on high dose enteral or parenteral therapy but with unacceptable side effects. Intrethecal infusions of analgesics have been increasingly utilized since the later 1980s for the treatment of persistent pain.

The purpose of this review is to provide research based clinical insight regarding the safe and appropriate use of the intrathecal infusion modality.

Long-term intrathecal infusion analgesia or long-term intrathecal or long-term intrathecal analgesic therapy has significantly progressed over the past 25 years. The evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignancy or neuropathic pain. The evidence is moderate for long-term management of persistent pain. Reasonably strong evidence exists for the use of long-term intrathecal analgesic therapy in alleviation of cancer pain; however, the evidence supporting long-term efficacy in persistent noncancer pain is less convincing.

Future studies are needed to better define the role of long-term intrathecal analgesic therapy in persistent pain, especially with respect to which pain conditions or subpopulations of patients are most responsive to ong-term intrathecal analgesic therapy, and which agents or combination of agents are most appropriate for which pain conditions or subpopulations of patients. Novel combinations of intrathecal analgesics such as clonidine and gabapentin deserve future study.

The current body of literature supports the use of intrathecal agents for the treatment of moderate or severe pain related to cancer and noncancer origins. Further clinical studies are needed to evaluate the efficacy and safety of new intrathecal drugs, the complications related to these devices, and the proper selection of patients to receive these treatments.

Key words: Intrathecal, morphine, baclofen, pump, implantable, infusion

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Intrathecal (IT) analgesia has emerged as a key therapeutic option for pain relief for patients who have failed all other treatment avenues as well as patients with adequate analgesia on high dose enteral or parenteral therapy but with unacceptable side effects. IT infusions of analgesics have been increasingly utilized since the later 1980s for the treatment of persistent pain. Intrathecal technology/devices along with preparation of a variety of intrathecal analgesic/co-analgesic agents have enabled a blossoming of intrathecal drug delivery. The 2007 ASIPP evidence-based practice guidelines in the management of chronic spinal pain concluded that the evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignancy or neuropathic pain. The evidence is moderate for long-term management of chronic pain (1).

Leonard Corning (2) is credited with neuraxial administration of local anesthetic in 1885, and morphine may have been administered spinally as early as 1901 (3). In 1971, specific opioid receptors were described (4) and in 1976, Yaksh and Rudy (5) demonstrated effective analgesia from intrathecal opioids in an animal model. Wang and colleagues (6) reported treating cancer pain with intrathecal morphine in 1979.

Opioids administered neuraxially, act at receptors in the substantia gelatinosa of the spinal cord dorsal horn to yield dose-dependent analgesia (7,8). Opioids may act through multiple mechanisms including inhibition of presynaptic neurotransmitter release from primary afferents via presynaptic inhibition of calcium channels (9-11). Furthermore, opening of G-protein-gates, K+ channels in the central nervous system (G-protein-regulated inwardly rectifying K+ channels [GIRKs]) may lead to postsynaptic neuronal hyperpolarization (8).

The MOR-expressing neurons in the dorsal horn of the spinal cord appear to be significantly involved in spinal opioid analgesia (12).

a. They activate opioid receptors at the central terminals of C-fibers in the spinal cord.
b. They activate opioid receptors on the second-order pain transmission cells, thus inhibiting ascending transmission of the pain signal.
c. Systemically administered morphine leads to an opioid-induced increase in spinal acetylcholine (Ach), and the opioid-induced spinal Ach—via activation of the spinal cholinergic system—contributes to opioid-mediated antinociception (13).

Upregulation of mu opioid receptors in the dorsal root ganglion may increase the antinociceptive potency of IT morphine more than 5 times (14). Finally, it is conceivable that some of the analgesia from IT morphine may be due to IT morphine causing spinal release of adenosine and subsequent spinal adenosine A1 receptor activation (15).

A variety of analgesic/co-analgesic agents have been utilized to provide spinal analgesia. The long-term spinal administration of agents to alleviate refractory persistent pain, the classic initial class of analgesics has been opioids.

After a review of literature from 2000 to 2006, and discussion, panelists from the Polyanlgesic Consensus Conference 2007, created an updated algorithm for the rational use of intrathecal opiod and nonopiod agents in patients with nonmalignant and end-of-life pain. The updated algorithm is represented in this discussion (16).

Intrathecal Drugs

Morphine remains the current gold standard for spinally administered analgesic agents and is the only opioid approved by the FDA for intrathecal delivery to treat chronic pain.

Anderson and Burchiel (17) published a prospective study in which 11 of 22 patients (50%) who completed 2 years of follow-up post-implantable drug delivery system (IDDS) implantation reported at least a 25% reduction in pain on a scale of 0 to 10 after 24 months of treatment with intrathecal morphine sulfate. In addition, the McGill Pain Questionnaire, visual analog scale measures of functional improvement and pain coping, and several subscales of the Chronic Illness Problem Inventory showed improvement throughout the follow-up period. They concluded that intrathecal morphine can be a safe, effective therapy for the management of severe, noncancer pain among a carefully selected patient population and may lead to long-term improvement in multiple domains of daily function.

Angel et al (18) reported on 11 patients between the ages of 29 and 81 years who had an IDDS implanted with morphine and were followed for up to 3 years with morphine. Eight of 11 (73%) were considered to have a good to excellent analgesic response and 3 of 11 (27%) were judged to have a poor analgesic response overtime (18).

Hassenbusch et al (19) performed a prospective evaluation of intrathecal opioid infusions in 18 noncancer patients with neuropathic pain over a 5-year period. Sixty-one percent (11/18) of patients had good

or fair pain relief with a mean follow-up 2.4 ± 0.3 years (0.8 – 4.7 years (19); average numeric pain scores decreased by 39% ± 4.3% (19).

Kumar and colleagues (20) prospectively followed 16 of 25 patients with severe, chronic noncancer pain refractory to conservative management who achieved more than 50% pain relief after a trial period of intrathecal morphine infusion. Follow-up evaluations were performed baseline and every 6 months over a period ranging from 13 months to 49 months (mean 29.14 month ± 12.44 months) (20). The best results were seen with deafferentation pain and mixed pain with 75% and 61% pain reduction respectively. Nociceptive pain patients had best pain relief initially (78% pain reduction) but it tended to diminish over time to 57% pain reduction at final follow-up. The average pain reduction for all groups after 6 months was 67.5% and at last follow-up, it was 57.5%. Kumar et al (20) considered 12/16 (75%) of the patients to be successes.

Thimineur and colleagues (21) prospectively evaluated long-term outcomes of IT opioid therapy in 38 patients who were with chronic noncancer pain IT pump recipients (PRs) and included 2 comparative groups. (One group of 31 IT candidated who either had an unsuccessful trial or declined IT therapy, and another group of 41 newly referred patients.)

The following data were analyzed at study entry, and at 6 monthly intervals for a 3-year period: Symptom Check List 90 (SLC-90), SF-36 Health survey, Beck Depression Inventory, McGill Pain Questionnaire (short form), Oswestry Disability Index, Pain Drawings, and Pain rating on visual analogue scale.

Data analysis suggests the study group of PRs had improvements in pain, mood, and function from baseline to 36 months. These same parameters improved among new referrals (less severe patients receiving conservative pain management) while non-recipients significantly worsened (21).

In a multicenter, open-label clinical study Rauck et al (22) evaluated a patient-activated IT morphine delivery system in 199 cancer patients who had either refractory pain or uncontrollable side effects. Pain decreased from a mean score of 6.1 to 4.2 at 1 month (31% decrease) and remained decreased through 13 months ($p < 0.05$). There was also a statistically significant reduction in drug toxicity and oral opioid requirements.

In 2002, Smith et al (23) prospectively performed a randomized clinical trial to evaluate comprehensive medical management (CMM) versus IDDS plus CMM for refractory cancer pain > 5 on a 0 to 10 scale.

Clinical success was defined as > or 20% reduction in VAS scores, or equal scores with > 20% reduction in toxicity. The main outcome measure was pain control combined with change of toxicity, as measured by the National Cancer Institute Common Toxicity Criteria, 4 weeks after randomization (23). Sixty of 71 IDDS patients (84.5%) achieved clinical success compared with 51 of 72 CMM patients (70.8%, $P = .05$) (23). IDDS patients more often achieved >/= 20% reduction in both pain VAS and toxicity (57.7% [41 of 71] v 37.5% [27 of 72], $P = .02$) (23). The mean CMM VAS score fell from 7.81 to 4.76 (39% reduction); for the IDDS group, the scores fell from 7.57 to 3.67 (52% reduction, $P = .055$) (23). The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the IDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, $P = .004$) (23). The IDDS group has significant reductions in fatigue and depressed level of consciousness ($P < .05$) (23).

Smith et al (24) performed a planned longitudinal prospective analysis of 30 of 99 (30%) patients who did not derive significant benefit from CMM by 6 months and crossed over to IDDS as part of the randomized clinical trial in 2002 (24). At the time of the crossover, the mean opioid dose was 320 mg of morphine or morphine equivalent per day with at least 1 adjuvant drug. Analgesia (on a scale of 0-10) and adverse effects (utilizing a "comprehensive toxicity score" from the National Cancer Institute [NCI] Common Toxicity Criteria [CTC]) were compared pre-IDDS implant and post-IDDS implant. The average pain score went from 6.2 ± 2.8 pre-IDDS implant to 4.5 ± 2.7 post-IDDS implant, for a 27% mean reduction in pain ($P = $).011). The average toxicity score went from 7.6 ± 4.8 pre-IDDS implant to 3.8 ± 24.2 post-IDDS implant, for a 51% mean reduction in toxicity ($P = 0.0001$). Overall, the evidence for intrathecal opioids in IDDS is strong for cancer pain and moderate for noncancer pain (Table 1).

Kumar and colleagues (20) reported multiple adverse effects of IT morphine with lethargy, fatigue, and sweating being among most common and lasting side effects. Other adverse effects reported include constipation, disturbed micturition/urinary retention, vomiting, pruritus, dysphoria, diarrhea, malaise, cold sweats, anxiety, nightmares, loss of appetite, dry mouth, myoclonic jerks/spasms, dizziness, headaches, sleep disturbances (e.g., insomnia), and sexual disturbances (e.g.

Table 1. *Intrathecal opioids for noncancer and cancer pain.*

Study	Participants	Follow-up	Intervention	Results	Conclusion
Non-cancer Pain					
Hassenbusch et al 1991 (19) prospective observational	18 patients with neuropathic noncancer pain.	0.8-4.7 years	Implantations of IDDS with morphine sulfate or sufentanil citrate.	Sixty-one percent (11/18) of patients had good or fair pain relief with mean follow-up 2.4 +/- 0.3 years (0.8-4.7 years). Average numeric pain scores decreased by 39% +/- 4.3%. Five of the 11 responders required lower opioid doses (12-24 mg/day morphine) and the remaining 6 patients required higher opioid doses (> 34 mg/day morphine)	Long-term intrathecal opioid infusions can be effective in treatment of neuropathic pain but might require higher infusion doses
Anderson and Burchiel 1999 (17) prospective observational	30 patients with mixed/ nociceptive/ deafferentation/ neuropathic noncancer pain. The participants had a mean age of 58 +/- 13 years and a mean pain duration of 8 +/- 9 years. Fifty-three percent of the study participants were women. Pain type was characterized as mixed neuropathic-nociceptive (15 of 30 patients, 50%), peripheral neuropathic (10 of 30 patients, 33%), deafferentation (4 of 30 patients, 13%), or nociceptive (1 of 30 patients, 3%).	2 years	Implantation of IDDS with morphine sulfate. Pharmacological side effects were managed medically by morphine dose reduction, addition of bupivacaine, or replacement of morphine with hydromorphone.	Overall, 50% (11 of 22 patients) of the population reported at least a 25% reduction in visual analog scale pain after 24 months of treatment. In addition, the McGill Pain Questionnaire, visual analog scale measures of functional improvement and pain coping, and several subscales of the Chronic Illness Program Inventory showed improvement throughout the follow-up period.	Continuous intrathecal morphine can be safe, effective therapy for the management of severe, nonmalignant pain among a carefully selected patient population and can result in long-term improvement in several areas of daily function.
Kumar et al 2001 (20) prospective observational	16 patients with nociceptive/ mixed/ deafferentation noncancer pain.	1-4 (mean 1.5) years	Implantation of IDDS with morphine sulfate.	The best long-term results were seen with deafferentation pain and mixed pain, with 75% and 61% pain reduction (visual analog scale), respectively. Nociceptive pain patients had best pain relief initially (78% pain reduction) but it tended to decrease over the follow-up period to 57% pain reduction at final follow-up. The average pain reduction for all groups after 6 months was 67.5% and at last follow-up, it was 57.5%.	The administration of intrathecal opioid medication for nonmalignant pain is justified in carefully selected patients.

Table 1. *continued*.

Study	Participants	Follow-up	Intervention	Results	Conclusion
Thimineur et al 2004 (21) prospective observational with 2 comparative groups	This study evaluated long-term outcome of IT opioid therapy in chronic non-malignant pain prospectively, and included 2 comparative groups to improve understanding of selection criteria and relative severity of intrathecal pump recipients (PRs). The study subjects included 38 PRs while the comparative groups included 31 intrathecal candidates who either had an unsuccessful trial or declined the IT therapy, and another group of 41 newly referred patients.	3 years	Implantation of IDD with multiple agents and/or combinations of analgesic agents. The following data were analyzed at study entry, and at 6 monthly intervals for a 3-year period: Symptom Check List 90 (SLC-90), SF-36 Health survey, Beck Depression Inventory, McGill Pain Questionnaire (short form), Oswestry Disability Index, Pain Drawings and Pain Rating on visual analogue scale.	Data analysis suggests the study group of PRs had improvements in pain, mood, and function from baseline to 36 months. The group of PRs also achieved significant pain relief (~27%). Baseline pain score from 0 to 10 8.4 (1.4) was reduced to 6.1 (0.6) at 36 months post-implantation ($P < 0.000001$).	The study showed that when patients with extremely severe pain problems are selected as pump candidates, they will likely improve with the therapy, however, their overall severity of pain and symptoms may still remain high.
Angel et al 1998 (18) prospective observational	11 patients with mixed/ neuropathic noncancer pain.	0.5-3 (mean 2.3)	Implantations of IDDS with morphine sulfate.	A good to excellent analgesic response was seen in 8 (73%) patients. In the remaining 3 patients (27%), the analgesic response was judged poor.	Intrathecal morphine infusion was found to be viable analgesic option for refractory pain.
Cancer Pain					
Smith et al 2002 (23) double-blind, placebo-controlled randomized clinical trial	202 patients were enrolled in an RCT of comprehensive medical management (CMM) versus implantable intrathecal drug delivery systems (IDDS) plus CMM. Entry criteria included unrelieved cancer pain (visual analog scale [VAS] pain scores >/= 5 on a 0 to 10 scale). Clinical success was defined as >/= 20% reduction in VAS scores, or equal scores with >/= 20% reduction in toxicity. The main outcome measure was pain control combined with change of toxicity, as measured by the National Cancer Institute Common Toxicity Criteria, 4 weeks after randomization. Neuropathic pain and mixed neuropathic-nociceptive pain were most common.	0.5 years	Implantations of IDDS starting with morphine but if inadequate analgesia other IT analgesics could be used per algorithm.	Sixty of 71 IDDS patients (84.5%) achieved clinical success compared with 51 of 72 CMM patients (70.8%, $P = .05$). IDDS patients more often achieved ≥ 20% reduction in both pain VAS and toxicity (57.7% [41 of 71] v 37.5% [27 of 72], $P = .02$). The mean CMM VAS score fell from 7.81 to 4.76 (39% reduction); for the IDDS group, the scores fell from 7.57 to 3.67 (52% reduction, $P = .055$). The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the IDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, $P = .004$).	The IDDS group had significant reductions in fatigue and depressed level of consciousness ($P < .05$). IDDS patients had improved survival, with 53.9% alive at 6 months compared with 37.2% of the CMM group ($P = .06$). IDDSs improved clinical success in pain control, reduced pain, significantly relieved common drug toxicities, and improved survival in patients with refractory cancer pain.

Table 1. *continued*.

Study	Participants	Follow-up	Intervention	Results	Conclusion
Rauck et al 2003 (22) prospective open-label study	Patients with refractory cancer pain or uncontrollable side effects were enrolled at 17 US and international sites in this prospective, open-label study. Pain relief, reduction in systemic opioid use, and reduction in opioid-related complications were analyzed both individually and together as a measure of overall success. One hundred forty-nine patients were enrolled and 119 were implanted.	Max 4.7 years (Data presented over 16 months post-implantations)	Implantation of IDDS featuring patient-activated delivery with morphine sulfate.	Average numeric analog scale pain decreased from 6.1 to 4.2 at 1 month and was maintained through month 7 ($P < .01$) and through month 13 ($P < .05$). Systemic opioid use was significantly decreased throughout the study ($P < .01$). Significant reduction in the opioid complication severity index was demonstrated at all 4 follow-up visits ($P < .01$). Overall success (≥50% reduction in numeric analog scale pain, use of systemic opioids, or opioid complication severity index) was reported in 83%, 90%, 85%, and 91% of patients at months 1, 2, 3, and 4, respectively.	This study demonstrated that patients with refractory cancer pain or intolerable side effects achieved better analgesia when managed with patient-activated intrathecal delivery of morphine sulfate via an implanted delivery system.

loss of libido, potency disturbances, amenorrhea). Ruan (25) reviewed the drug-related side effects of long-term intrathecal morphine therapy and also reported on respiratory depression, edema, hyperalgesia, and catheter tip inflammatory mass formation.

Johansen et al (26) reported that high levels of IT morphine-3-glucuronide have been associated with drowsiness, hyperalgesia, allodynia, and myoclonus. Slowly increasing chronic respiratory depression may rarely occur with long-term intrathecal morphine therapy (27). Chronic respiratory depression may be suspected clinically in patients receiving long-term IT morphine administration who exhibit escalating morphine dose without improved analgesia, increasing fatigue, exercise dyspnea, and a progressive step-wise decline in pulmonary function (27).

Other adverse effects from IT morphine mat include hypothalamic-pituitary axis suppression with resultant low testosterone/estrogen and diminished libido (28, 29), noncardiac pedal edema (28), and granuloma formation.

Hydromorphone

Hydromorphone, a semisynthetic hydrogenated ketone of morphine, is a more potent and faster-acting analgesic than morphine due to its greater lipophilic properties.

Anderson et al (30) conducted a retrospective review of patients with chronic nonmalignant pain managed with intrathecal hydromorphone after failure of intraspinal morphine. Analgesic response was improved by a least 25% in 6 of 16 patients who were switched to hydromorphone because of poor pain relief (30).

Hydromorphone IT infusions may offer a viable therapeutic alternative to IT morphine for patients with intractable pain not alleviated by morphine or with intolerable side effects to morphine. This medication, in particular, is appropriate for use in patient-controlled IDDS for treating breakthrough pain because of its relatively greater analgesic potency and fewer adverse side effects when compared to morphine. Intrathecal morphine and IT hydromorphone, in a dose 20% of that of morphine, induce an equianalgesic response (25). Intrathecal hydromorphone improved the incidence of side effects, including nausea and vomiting, pruritus, and sedation, in most patients with chronic nonmalignant pain who had shown poor analgesic response to IT morphine. Short-term administration of IT hydromorphone mitigated peripheral edema in patients previously treated with IT morphine (30, 31). High-dose IT hydromorphone may also lead to granuloma formation (32).

Allen et al (33) performed toxicity experiments for spinal opioids in dogs. They concluded that in-

trathecal opiate-induced granulomas are not strictly dependent on opioid receptor activation, and opiates at equianalgesic doses present different risks for granuloma formation (33).

Local Anesthetics

Van Dongen et al (34) found that the addition of IT bupivacaine to opioids resulted in adequate analgesia in 10 of 17 cancer patients who failed IT opioid therapy alone. The mean follow-up in this study was 112 days. In a later, double-blind, randomized trial comparing IT morphine alone to IT morphine and bupivacaine in 20 cancer patients, the same group found the combination group developed less opioid tolerance than the morphine-only group (35). Five patients in the IT morphine group switched to the combination group secondary to inadequate analgesia; 3 of 15 patients who received morphine and bupivacaine experienced subjective weakness that did not interfere with walking. The authors concluded the combination of IT bupivacaine and morphine provided synergistic analgesic effects.

Intrathecal combinations of local anesthetics and opioids have led to similar beneficial results reported for in noncancer pain (36). Krames (37) found that the addition of bupivacaine to IT opioids either decreased opioid side effects or enhanced analgesia in 77% of 13 patients with noncancer pain treated with an IT infusion pump, with a mean follow-up of almost 1 year.

However, a multicenter, double-blind randomized study (38) found that the addition of bupivacaine (up to 8 mg/day) did not provide better pain relief than opioids alone. Although a number of authors have reported improved pain relief when bupivacaine was added to the IT drug mixture, all but 1 study are uncontrolled and nonrandomized case studies (39).

Alpha-2 Agonists

Alpha-2 adrenergic receptors play a key role in analgesic effects mediated at peripheral, spinal, and brainstem sites.

Presynaptically in the spinal cord, they bind to alpha-2 receptors on small primary afferent neurons, resulting in hyperpolarization and diminished release of neurotransmitters involved in relaying pain signals. Alpha-2 agonists hyperpolarize the cell by increasing potassium conductance through Gi coupled potassium channels on postsynaptic neurons (40). Alpha-adrenergic agonists also activate spinal cholinergic neurons, which may potentiate their analgesic effects.

Clonidine is the most studied and only FDA-approved alpha-2 agonist for intraspinal use. Intrathecal clonidine has been reported to provide significant analgesia alone or in combination with opioids for neuropathic pain, cancer pain, or complex regional pain syndrome (41,42). Rainov et al (43) reported excellent or good results at 2-year follow-up visits in 73% of patients in a prospective, open-label study evaluating combination IT therapy in 26 adults with failed back surgery syndrome. Sixteen patients received clonidine as part of their IT therapy, half of which were in combination with morphine and bupivacaine. The mean dose was 0.06 mg/day. In a double-blind, placebo-controlled study Siddall et al (44) assessed the efficacy of IT morphine or clonidine, alone or combined for up to 6 days, in 15 patients with central pain secondary to spinal cord injury. The authors found the combination of clonidine and morphine provided significantly better pain relief than saline (37% vs. 0% reduction) or either drug alone (20% reduction for morphine, 17% decrease for clonidine).

Rudich et al (45) found no loss in clonidine concentration during the time between refills (35 +/- 13 days), and no correlation between clonidine concentration and time interval between refills using HPLC analysis of 20 paired samples from 3 patients in a stability study of clonidine-hydromorphone mixtures. They concluded that clonidine, mixed with hydromorphone, is stable when delivered by implantable intrathecal pump for long-term use (45).

Adverse effects which may be associated with spinal clonidine include nausea, dizziness, confusion, sedation (likely via alpha-2-adrenergic actions in the locus ceruleus), hypotension/orthostasis, bradycardia, and dry mouth. Clonidine decreases heart rate by a presynaptic mediated inhibition of norepinephrine release and by a direct depression of atrioventricular nodal conduction (46) after systemic absorption. Depression, insomnia, and night terrors have been reported to develop in association with intraspinal clonidine (47). Furthermore, rebound hypertension has been observed after abrupt discontinuation of intraspinal clonidine (48).

Ziconotide

Ziconotide (formerly SNX-111, Neurex Pharmaceuticals, Menlo Park, CA) is the synthetic equivalent of ω-conopeptide MVIIA, a 25–amino-acid polybasic peptide present in the venom of conus magus, a marine snail (49). Ziconotide produces potent antinociceptive

effects (50) by selectively binding to N-type voltage-sensitive calcium channels (51,52) on neuronal somata, dendrites, dendritic shafts, and axon terminals, thus blocking neurotransmission from primary nociceptive afferents (53).

In efforts to assess the safety and efficacy of IT ziconotide in patients with cancer or AIDS who have refractory pain; Staats and colleagues (53) performed a double-blind, placebo-controlled, randomized trial at 32 study centers in the United States, Australia, and the Netherlands.

Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of non-responders to the opposite treatment group. Mean percentage change in VASPI score from baseline to the end of the initial titration period. Of the population evaluated, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; $P = .63$, based on mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($P = .18$). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P < .001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($P < .001$). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo ($P = .001$). Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS (53).

In an attempt to reduce side effects and increase tolerability, Rauck et al (54) conducted a double-blind, placebo-controlled study using a slower titration schedule and lower maximum dose than previous studies in 220 patients with chronic, noncancer refractory to conventional treatment. VAS pain scores improved by 15% in the ziconotide group vs. 7% in the placebo group, at the end of the 3-week treatment period. During the treatment period, 12% of ziconotide patients reported adverse effects. Overall, the evidence for intrathecal ziconotide in IDDS is strong for short-term improvement of chronic pain (Table 2).

Possible side effects of ziconotide may include:

- an allergic reaction,
- nausea, vomiting, seizures, fever, headache, and/or stiff neck (e.g. meningitis),
- a change in mental status (extreme tiredness, asthenia, confusion, disorientation or decreased alertness),
- a change in mood or perception (hallucinations, unusual feelings in the mouth),
- postural hypotension, abnormal gait, urinary retention, nystagmus/amblyopia
- drowsiness/somnolence,
- dizziness or lightheadedness, weakness, or
- visual problems (e.g. double vision).

Vestibular side effects may be due to ziconotide blocking N-type calcium channels in the granular cell layer of the cerebellum (55).

The Polyanalgesic Conference 2007, a panel of experts known for their expertise in IT therapy, felt, based on relevant new literature and clinical experience, that ziconotide should be upgraded to a first-line intrathecal agent (16).

Baclofen

Baclofen (Lioresal) is the p-chlorophenyl derivative of GABA. Baclofen is a GABA-B agonist that has been used for muscle spasms, spasticity, and neuropathic pain. Baclofen is a racemic mixture with L-baclofen being the active form. Baclofen has both presynaptic and post-synaptic actions. At the presynaptic site, baclofen decreases calcium conduction with resultant decreased excitatory amino acid release. At the post-synaptic site, baclofen increases potassium conductance, leading to neuronal hyperpolarization. Additionally, baclofen may inhibit the release of substance *P*. Use of baclofen appears to lead to marked facilitation of segmented inhibition.

Intrathecal baclofen infusions have been used to treat spasticity since the mid-1980s and IT baclofen administration via an implanted device is approved by the Food and Drug Administration (FDA) for this indication. In a Cochrane review of pharmacological interventions for spinal cord injury-induced spasticity, Tarrico et al (56) concluded that only IT baclofen has been proven effective. Two studies (14 SCI patients) showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth score and activities of daily living [ADL] performances), compared to placebo, without any adverse effect (56).

Table 2. *Intrethecal ziconotide for pain*.

Study	Participants	Follow-up	Intervention	Results	Conclusion
Intrathecal Ziconotide for Pain					
Staats et al 2004 (53) prospective randomized trial	Patients were 111 individuals ages 24 to 85 years with cancer or AIDS and a mean Visual Analog Scale of Pain Intensity (VASPI) score of 50 mm or greater. Patients were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment.	0.03 year (11 days)	Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of non-responders to the opposite treatment group.	Of the population evaluated, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; $P = .63$, based on mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($P = .18$). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P < .001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($P < .001$). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo $P = .001$).	Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.
Rauck et al 2006 (54) randomized, double-blind, placebo-controlled study	Patients randomized to ziconotide (n = 112) or placebo (n = 108) and predominantly with neuropathic noncancer pain were started IT infusion at 0.1 µg/hour (2.4 µg/day), increasing gradually (0.05–0.1 µg/hour increments) over 3 weeks.	0.06 year (3 weeks)	Implantation of IDDS with ziconotide.	Patients' baseline Visual Analogue Scale of Pain Intensity (VASPI) score was 80.7 (SD 15). Statistical significance was noted for VASPI mean percentage improvement, baseline to Week 3 (ziconotide [14.7%] vs. placebo [7.2%; $P = 0.036$]).	Slow titration of ziconotide, a nonopioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in 2 previous controlled trials that used a faster titration to a higher mean dose (Rauck, 2006). Eighty seven percent of patients receiving ziconotide expressed a desire to continue receiving the medication in an open-label follow-up study.

Van Hilten et al (57) performed a double-blind, randomized, controlled crossover trial of bolus intrathecal injections of 25, 50, and 75 microgram of baclofen and placebo in patients with complex regional pain syndrome. Changes in the severity of dystonia were assessed by the woman and by an investigator after each injection. In the second phase of the study, 6 of the women received a subcutaneous pump for continuous intrathecal administration of baclofen and were followed for 0.5 to 3 years. In 6 women, bolus injections of 50 and 75 µg of baclofen resulted in complete or partial resolution of focal dystonia of the hands but little improvement in dystonia of the legs. During continuous therapy, 3 women regained normal hand function, and 2 of these 3 women regained the ability to walk. Three patients experienced marked reductions in pain, 4 in paresthesias and 2 with numbness. In 1 woman who received continuous therapy, the pain and violent jerks disappeared and the dystonic posturing of the arm decreased. In 2 women the spasms or restlessness of the legs decreased, without any change in the dystonia. Van Hilten and colleagues (57) concluded that in some patients, the dystonia associated with complex regional pain syndrome responds markedly to intrathecal baclofen.

Herman et al (58) performed double-blind, randomized, and placebo-controlled trials to assess the efficacy of acute IT baclofen on chronic, dysesthetic, and spasm-related pain (SRP) among patients with spinal spasticity (i.e., multiple sclerosis, spinal cord injury, and transverse myelitis). IT baclofen significantly suppressed dysesthetic pain and SRP with temporal dissociation affecting pinch-induced and musculoskeletal (low back) pain.

However, in a series involving 16 patients with mixed pain syndromes secondary to spinal cord injury, Loubser and Akman (59) reported an 83% reduction in musculoskeletal pain symptoms but no appreciable decrease in neuropathic pain 12 months after baclofen pump implantation. Intrathecal baclofen has also been reported to relieve neuropathic pain secondary to failed back surgery syndrome, amputation, and plexopathy (60-63). Strong evidence exists to support the use of IT baclofen for spasticity-related pain, and mixed evidence for central and neuropathic pain.

Adverse side effects of therapeutic doses of baclofen include drowsiness/sedation, flaccidity, weakness, headache, confusion, lightheadedness, hypotension, weight gain, constipation, nausea, urinary retention, and sexual dysfunction (64). Overdose of baclofen can lead to respiratory depression, seizures, and if not promptly treated, death. Intravenous physostigmine in incremental 1-2 mg boluses may be beneficial in some cases of baclofen overdose (65). Abrupt cessation of baclofen infusion can also be life threatening as well. Signs and symptoms may include hallucinations, anxiety, tachycardia, seizures and potentially muscle rigidity, fever, and labile blood pressure with progression to DIC, rhabdomyolysis, and death if untreated.

Dyspnea associated with increased muscle tone may be an important indicator of baclofen withdrawal in patients with IT baclofen therapy which may occur due to the abrupt onset of adductor spasms of the vocal cords (66). Pruritus, a common symptom following IT baclofen withdrawal, is associated with the inhibitory effects of baclofen on the release of substance *P* at the spinal level (67). While increased spasticity is usually caused by drug tolerance or irritant factors, pruritus appears to be a good clinical indicator of baclofen withdrawal. Pruritus was reported in 10 of 23 cases of IT baclofen withdrawal after the first 3 months after pump implantation. Dysfunction of the infusion system may provoke pruritus in patients receiving IT baclofen (16). Treatment consists of supportive measures and restoration of IT baclofen, and there is some evidence to suggest that replacement with oral baclofen may not always be adequate to control withdrawal symptoms (68).

Deer and colleagues (69) reported 2 cases of inflammatory mass in patients receiving baclofen as a sole intrathecal agent.

"Intrathecal Cocktails"

Mixtures or combinations of IT analgesic agents are even less well studied than single agents; however, various combinations continue to be utilized in clinical practice and were recognized by the 2007 polyanalgesic consensus conference. High-performance liquid chromatography (HPLC) analysis revealed that morphine sulfate combined with bupivacaine hydrochloride and clonidine hydrochloride incubated in SynchroMed implantable pumps (SynchroMed, Medtronic Inc., Minneapolis, MN, USA) at 37°c for 90 days remained stable with more than 96% of the original concentration intact. Combinations of morphine or hydromorphone with bupivacaine have been recognized to be stable (70,71).

Ziconotide at concentrations of less than 1 mcg/mL is not all that stable but is stable at higher concentrations. Morphine and hydromorphone facilitate ziconotide degradation, thus the 2007 polyanalgesic consensus conference suggestions limiting the con-

centration and dose of opioid when utilizing opioid/ziconotide admixtures (72). Clonidine, 2 mcg/mL combined with ziconotide is stable (roughly 90% stable to 60 days) whereas bupivacaine/ziconotide is somewhat less stable (73,74). Ziconotide/ baclofen admixtures are 80% stable over 30 days (and even more stable when compounded with powdered baclofen) (75). A ziconotide/clonidine/morphine admixture was 70% stable for 20 days (73).

Adverse Effects of Long-term Intrathecal Infusion Therapy

Turner et al (76) described complications derived from 10 published reports. Non-pharmacological biological complications included wound infection 12% across in 3 studies, meningitis 2% in 3 studies, and pump malposition in 17% in 2 studies. CSF leaks during catheter placement leading to postdural headache were not commonly reported but clearly represent another complication (76). Among the 10 studies, 7 studies (20,43,77-81) did not mention this complication at all, 2 (17,82) mentioned it, but did not provide both the number of patients assessed for this complication and the number of patients who had the complication, and 1 (18) reported that no patients had it.

There were a number of intrathecal granulomas at the tip of the intrathecal catheter some of which were large enough to cause spinal cord compression and neurologic dysfunction such as urinary incontinence and paraparesis or paraplegia (76). Traumatic syrinx, local erythema and edema in the area of the abdominal wall pocket and lower extremity edema, transverse myelitis due to catheter-tip infection, postdural puncture headache, diplopia, cranial nerve palsy and intracranial subdural hematoma, dissociative mental state, symptoms of withdrawal, and patient self-draining of morphine have been reported (76).

Intrathecal granuloma formation is a serious complication that carries the potential to produce spinal cord compression and paralysis distal to the mass. Over 100 cases have been reported, the first of which was in 1991 (83,84).

The phenomenon appears to be a function of concentration (>25mg/mL), daily dose (>10mg/d), and duration of therapy. However, 39% of cases occurred with morphine concentrations less than 25mg/mL, and 30% received daily morphine doses less than 10 mg/d. Some were noted within 1 month of the initiation of therapy (85).

Jones and Rawlins (86) have reviewed the diagnosis of intrathecal infusion pump system failure. There are many possible causes for a change in a catheter's performance including micro fracture, kinking, disconnection, breakage, dislodgement, migration to the epidural space or out of spine completely, complete or partial occlusion from tip fibrosis, hygroma, or inflammatory mass (Table 3) (86).

Although the frequency of complications with implanted intrathecal pump systems may be decreasing, such complications continue to develop, are not always obvious, and may manifest with subtle symptoms. A number of diagnostic procedures are useful in determining the cause of failure (Table 4) (86).

Deer (87) prospectively studied a total of 208 patients who underwent imaging over a period of 34 weeks. Intrathecal granulomas were identified in 3% of patients imaged in this series. Eighty percent of the patients were asymptomatic. MRI imaging remains the diagnostic method of choice for most patients, and can be done safely when scans are taken at the level of the catheter tip (87). Given the low incidence of granulomas with intrathecal catheters, routine imaging to identify granulomas is not warranted (87). Deer et al (16) recently published the Polyanalgesic Consensus Conference 2007: Recommendation for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery. The interdisciplinary expert panel of both physicians and non-physicians in the field of intrathecal therapies convened in 2007 to update previous recommendations/guidelines put forth in 2000 and 2003 after review of the literature from 2000 to 2006 and discussion. Line 1 which is the "first-line" agents for intrathecal analgesia and has 3 analgesics: a) morphine-—the only opioid which is ap-

Table 3. *Causes of pump failure.*

- Change in performance or failure of the catheter
  - → Micro-fracture
  - → Pinhole leak
  - → Disconnection
  - → Breakage
  - → Migration
  - → Partial occlusion
  - → Tip fibrosis/granuloma
  - → Inflammatory mass
- Unexpected battery depletion
- Component or motor failure
- Catheter access port failure

Reproduced from Jones and Rawlings (86), 2005

Table 4. *Diagnostic approaches*.

• Initial evaluation, including patient history will often identify the source of the problem
• Verification of pump contents, volume, and pump settings is the critical initial step
• Plain X-Ray (PA and LAT to visualize the entire catheter)
• Serial x-ray or fluoroscopy to confirm that the pump roller is moving at the expected rate
• Magnetic Resonance Imaging (MRI) study
• Catheter access port aspiration
• Nuclear medicine scan
• Fluid collection assay

Reproduced from Jones and Rawlings (86), 2005

Table 5. *Concentrations and doses of intrathecal agents recommended by the polyanalgesic consensus panelists, 2007*.

Drug	Maximum concentration	Maximum dose/day
Morphine	20 mg/mL	15 mg
Hydromorphone	10 mg/mL	4 mg
Fentanyl	2 mg/mL	No known upper limit
Sufentanil	50 µg/mL (not available for compounding)	No known upper limit
Bupivacaine	40 mg/mL	30 mg
Clonidine	2 mg/mL	1.5 mg
Ziconotide	100 µg/mL	19.2 µg (Elan recommendations)

proved by the Federal Drug Administration (FDA) for long-term IT administrations; b) hydromorphone (an alternative "first-line" IT opioid which is more potent with less adverse effects); and ziconotide (Prialt®) added as a "first-line" agent in 2007 and the only nonopioid analgesic approved by the FDA for long-term IT use. Ziconotide is recommended as a Line 1 drug in the 2007 algorithm for nociceptive, mixed, and neuropathic pain (Fig.1) (16). In efforts to minimize toxicities/adverse effects including the concentration-dependent risk of catheter-tip granuloma formation, the panel has proposed titration to an a priori upper limit that has been determined from clinical experience (Table 5).

Conclusion

Long-term intrathecal infusion analgesia or long-term intrathecal analgesic therapy (LTIAT) has significantly progressed over the past 25 years. The evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignancy or neuropathic pain. The evidence is moderate for long-term management of persistent pain. Reasonably strong evidence exists for the use of LTIAT in alleviation of cancer pain; however, the evidence supporting long-term efficacy in persistent noncancer pain is less convincing.

Future studies are needed to better define the

2007 Polyanalgesic Algorithm for Intrathecal Therapies

Line #1:	**(a)** morphine	↔	**(b)** hydromorphone	↔	**(c)** ziconotide
Line #2:	**(d)** fentanyl	↔	**(e)** morphine/hydromorphone + ziconotide	↔	**(f)** morphine/hydromorphone + bupivacaine/clonidine
Line #3:	**(g)** clonidine	↔	**(h)** morphine/hydromorphone/fentanyl bupivacaine + clonidine + ziconotide		
Line #4:	**(i)** sufentanil	↔	**(j)** sufentanil + bupivacaine + clonidine + ziconotide		
Line #5:	**(k)** ropivacaine, buprenorphine, midazolam meperidine, ketorolac				
Line #6:	***Experimental Drugs*** **(l)** gabapentin, octreotide, conopeptide, Neostigmine, Adenosine, XEN2174, AM336, XEN, ZGX 160				

Fig 1. *Recommended algorithm for intrathecal polyanalgesic therapies, 2007. Line 1: Morphine (a) and ziconotide (c) are approved by the Food and Drug Administration of the United States for intrathecal analgesic use and are recommended for first line therapy for nociceptive, mixed, and neuropathic pain. Hydromorphone (b) is recommended based on clinical widespread usage and apparent safety. Line 2: Because of its apparent granuloma sparing effect and because of its wide apparent use and identified safety, fentanyl (d) has been upgraded to a line 2 agent by the consensus conference when the use of the more hydrophilic agents of line 1 (a,b) result in intractable supraspinal side effects. Combinations of opioid + ziconotide (e) or opioid + bupivacaine or clonidine (f) are recommended for mixed and neuropathic pain and may be used interchangeably. When admixing opioids with ziconotide, attention must be made to the guidelines for admixing ziconotide with other agents. Line 3: Clonidine (g) alone or opioids such as morphine/hydromorphone/fentanyl with bupivacaine and/or clonidine mixed with ziconotide (h) may be used when agents in line 2 fail to provide analgesia or side effects occur when these agents are used. Line 4: Because of its proven safety in animals and humans and because of its apparent granuloma-sparing effects, sufentanil alone (i) or mixed with bupivacaine and/or clonidine plus ziconotide (j) is recommended in this line. The addition of clonidine, bupivacaine, and or ziconotide is to be used in patients with mixed or neuropathic pain. *In patients with end of life, the panelists felt that midazolam and octreotide should be tried when all other agents in lines 1–4 have failed. Line 5: These agents (k), although not experimental, have little information about them in the literature and use is recommended with caution and obvious informed consent regarding the paucity of information regarding the safety and efficacy of their use. Line 6: Experimental agents (l) must only be used experimentally and with appropriate Independent Review Board (IRB) approved protocols (16).*

role of LTIAT in persistent pain, especially with respect to which pain conditions or subpopulations of patients are most responsive to LTIAT, and which agents or combination of agents are most appropriate for which pain conditions or subpopulations of patients. Novel combinations of intrathecal analgesics (e.g. Ketamine and clonidine) (88) may deserve future study. As our ability to evaluate which various nociceptive mechanisms are playing a significant analgesic role and which patients improve, we may become better at tailoring specific intrathecal analgesics for specific patients/circumstances. For instance, it is conceivable that it may be useful to include intrathecal clonidine in an IDDS for a patient with persistent neuropathic pain and high levels of dorsal root ganglia brain derived nerve growth factor (BDNF) (89).

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