12-1-2021

Combination Intrathecal Drug Therapy Strategies for Pain Management

Jay Karri
Baylor College of Medicine

Mani Singh
NewYork-Presbyterian Hospital at Columbia and Cornell

Devas J Modi
NewYork-Presbyterian Hospital at Columbia and Cornell

Vwaire Orhurhu
University of Pittsburgh Medical Center

Caleb Seale
University of Texas Health Sciences Center at San Antonio

Pain Physician 2021; 24:549-569 • ISSN 1533-3159

Narrative Review

Combination Intrathecal Drug Therapy Strategies for Pain Management

Jay Karri, MD[1], Mani Singh, MD[2], Devas J. Modi, MD[2], Vwaire Orhurhu, MD[3], Caleb Seale, MD[4], Michael Saulino, MD[5], Anuj Marathe, BBA[1], Darrell Vydra, MD[4], Jonathan M. Hagedorn, MD[6], Brian Bruel, MD[7], and Alaa Abd-Elsayed, MD[8]

From: [1]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX; [2]Department of Rehabilitation and Regenerative Medicine, NewYork-Presbyterian Hospital at Columbia and Cornell, New York, NY; [3]Department of Anesthesia, Division of Pain Medicine, University of Pittsburgh Medical Center, Susquehanna, PA; [4]Department of Physical Medicine and Rehabilitation, University of Texas Health Sciences Center at San Antonio, San Antonio, TX; [5]Department of Rehabilitation Medicine, Moss Rehab and Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; [6]Department of Anesthesiology and Perioperative Medicine, Division of Pain Medicine, Mayo Clinic, Rochester, MN; [7]Department of Physical Medicine and Rehabilitation, McGovern Medical School and Cy Pain and Spine PLLC, Houston, TX; [8]Department of Anesthesia, Division of Pain Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

Address Correspondence:
Jay Karri, MD
100 E. Redwood, Apt 2521
Baltimore, MD 21202
E-mail: jaykarri@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: MS is a clinical investigator for Flowonix, Medtronic, and Bioness, receives in-kind speaker's fees from Ipsen and Medtronic, and holds two neuromodulation patents. JMH is a consultant for Abbott, Boston Scientific, and Nevro. BB is a consultant for Medtronic, Abbott,

Background: Numerous combination intrathecal drug therapy (CIDT) strategies exist and are utilized for varying pain syndromes, typically when monotherapy dose escalation or medication alternation is deemed untenable or unfeasible. Unfortunately, the supportive evidence basis for the use of these strategies and specific drug combinations is generally lacking and unclear, with many medications being used for off-label indications.

Objectives In this manuscript, we provide a robust exploration and analysis of the literature to provide an evidence-based narrative for the use of CIDT strategies in regard to clinical indications, pharmacologic parameters, specific drug combinations, safety profiles, and future directions.

Study Design: Narrative review.

Methods: This was an evidence based narrative performed after extensive review of the literature.

Results: Variances in intrathecal pharmacokinetics and pharmacodynamics are utilized advantageously with CIDT strategies to achieve improved analgesic benefit; however, appropriate use may be limited by increased or compounded risk of adverse effects. The supportive evidence for CIDT use for chronic pain conditions is largely lacking and limited to small, uncontrolled, observational studies, with many having various confounding factors, including a lack of standardized dosing. The most evidenced CIDT strategies include polyanalgesia with morphine-ziconotide, opioid-clonidine, and morphine-bupivacaine. Notably, in addition to pain relief, morphine-bupivacaine has been shown to decrease early opioid escalation requirements.

Limitations: The supportive evidence for CIDT use for chronic pain conditions is largely lacking and limited to small, uncontrolled, observational studies, with many having various confounding factors including a lack of standardized dosing.

Conclusions: CIDT strategies and polyanalgesia combinations can be effective for treating various patient populations with chronic pain. The appropriate use of these strategies may be limited by increased or compounded risk of adverse effects, both of which are highly patient and scenario dependent. Therefore, practitioners should maintain a particularly low threshold of suspicion for adverse effects in patients with CIDT such that safety profiles associated with this therapy can be favorably maintained.

Key words: Intrathecal, polyanalgesia, chronic pain, ziconotide, morphine, clonidine, bupivacaine

Pain Physician 2021: 24:549-569

Boston Scientific, Flowonix and TerSera. AA-E is a consultant for Medtronic, StimWave, Avanos, and Sollis. Remaining authors certify that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-26-2021
Revised manuscript received: 07-20-2021
Accepted for publication: 08-16-2021

Free full manuscript: www.painphysicianjournal.com

Intrathecal drug delivery is a well-studied strategy for the management of various chronic pain conditions (1-4). While morphine and ziconotide are the only FDA-approved intrathecal medications for treating chronic pain, there exist several additional medications that are utilized for off-label indications (1,2,5). Furthermore, there exist numerous combinations of intrathecal medications that are utilized for varying pain syndromes, typically if monotherapy dose escalation or medication alternation is deemed untenable or unfeasible. Expert consensus and societal guidelines, mainly from the Polyanalgesic Consensus Conference (PACC), provide recommendations regarding the use of combination intrathecal drug therapy (CIDT) strategies (1,6) (Table 1). However, the supportive evidence basis for the use of such strategies and specific drug combinations themselves is generally lacking and unclear. In this manuscript, we provide a robust exploration and analysis of the literature for the use of CIDT strategies in regard to clinical indications, pharmacologic parameters, specific drug combinations, and safety profiles.

Clinical Indications

Appropriate patient selection and disease-specific considerations are imperative to achieve good outcomes for intrathecal drug delivery (1-4). Selection criteria, which include psychological evaluation, social support determination, illness severity, and life expectancy, especially in the cancer population, have previously been discussed extensively (1). Upon meeting these criteria, intrathecal drug therapy is most clearly indicated for various etiologies of pain phenomena that are refractory to other measures of pain management, including spinal cord stimulation and/or surgery, or if surgery is unfeasible (7-12). In particular, this includes chronic malignant or nonmalignant pain that is neuropathic, nociceptive, or mixed in origin. Commonly indicated pain syndromes, as determined by PACC recommendations, include axial neck or low back pain, failed back surgery syndrome, abdominal and/or pelvic pain, extremity pain, complex regional pain syndrome, trunk pain, cancer pain either from direct tumor invasion or secondary to chemotherapy, or conditions with opioid efficacy but limited by intolerable side effects (1).

For those with chronic nonmalignant pain, the evidence suggests better outcomes utilizing intrathecal drug therapy for treating nociceptive pain relative to neuropathic pain or deafferentation pain syndromes (13). While the evidence for cancer pain is more extensive, cancer-related pain is often complex and manifests with clinical features of both nociceptive and neuropathic pain. For instance, many soft tissue tumors can result in neuropathic and visceral pain, while those with bone metastases will present with nociceptive pain. Regardless, fair evidence supports the use of CIDT for both types of pain related to cancer (14-17). Studies exploring CIDT strategies and combinations for use in cancer pain are challenging given the vast heterogeneity of discrete pain syndromes. Therefore, there exists a dearth of robust primary evidence exploring specific intrathecal strategies for specific cancer cohorts.

In characterizing pain syndromes, patients with localized pain, regardless of the type or etiology, are thought to be especially amenable to intrathecal therapy. This is secondary to our understanding that precision catheter tip placement proximal to the implicated nociceptive focus can provide direct necessary analgesic benefit. Previously, it had been demonstrated that catheter placement as high as upper cervical levels helped successfully treat chronic pain syndromes with intrathecal drug delivery (17). While patients with diffuse and non-localizable pain were traditionally thought to be poor responders, more recently, CIDT strategies have been noted to have roles in providing pain relief in such patients, as evidenced by the latest PACC recommendations (1). Therefore, a sophisticated appreciation for the supportive evidence of CIDT strategies is imperative to help treat patients with most complex pain conditions that may be refractory to intrathecal monotherapy. The most evidenced indication for CIDT use, however, exists for the use of adjunct local anesthetics to mitigate dose escalation of intrathecal opioids.

Pharmacologic Parameters

Intrathecal Pharmacokinetics

A nuanced appreciation for intrathecal pharmacokinetics and pharmacodynamics is imperative for safe and efficacious utilization of CIDT (1-4). Pharmacokinetics profiles of intrathecal drugs are governed by the medications' size, baricity, and lipophilicity (13). Drugs with large molecular sizes, high baricity, and high lipophilic profiles are less vulnerable to cerebrospinal fluid (CSF) flow and have limited rostral and caudal dispersion. In contrast, drugs with opposite properties have more extensive CSF flow and produce their effects far beyond the catheter tip (18-20). Notably, ziconotide is well recognized as having the greatest CSF dispersion and is particularly beneficial in treating diffuse pain (1,2,21). Unfortunately, primary studies exploring these drug dispersion patterns are limited to porcine studies, with comparable studies lacking in humans (22). In humans, CSF-specific drug dispersion is thought to be more complex still given endogenous CSF flow currents, gravity-dependent pressures, and many other variables. Nonetheless, this understanding of intrathecal pharmacokinetics is utilized to dictate clinical practice patterns (18-20).

Variances in intrathecal pharmacokinetics are utilized advantageously with CIDT strategies. Namely, the concomitant use of drugs with opposing pharmacokinetic profiles can allow for both local and diffuse spread to obtain local and distal analgesic benefit, respectively (1-4,18-20). Such strategies are particularly incorporated for persons with malignant chronic pain phenomena wherein catheter tip placement near tumor burden allows for the use of local lipophilic agents like bupivacaine to produce at-level analgesia (3-6). Similarly, hydrophilic agents like morphine or ziconotide can help produce more diffuse and central analgesic benefit (1,3-5). It must be noted that drug dispersion within the intrathecal space is also a product of infusion mechanisms with bolus and faster rate infusions theorized to produce more widespread drug distribution (22). In addition to pharmacokinetically optimizing intrathecal drug combinations, complex chronic pain pathologies may warrant the utilization of varying drug targets and mechanisms to achieve necessary analgesia.

Intrathecal Pharmacodynamics

Free nerve endings in the periphery transmit noxious stimuli to the spinal cord via afferent neurons. Intrathecal medications modulate these stimuli at the spinal level to prevent them from propagating via ascending pain pathways which synapse at the thalamus (23). As shown in Table 2, intrathecal medications act upon varying targets, mostly located within dorsal horn neurons, to collectively prevent the release of noxious neurotransmitters like glutamate, substance-P, and others (24). However, the different specific pain mechanisms employed by these medications make them each particularly beneficial in achieving analgesic benefit. A sophisticated understanding of the pharmacodynamic synergism with CIDT medications, however, has yet to be clearly delineated. However, it is generally accepted that intrathecal polyanalgesia contributes to pain relief as a result of activating a multitude of differing mechanisms along the afferent nociceptive pathway (1-5,11,24).

Table 1. *Combination intrathecal drug delivery strategy recommendations, as adapted from the 2017 PACC guidelines (1).*

Type of Pain	Level of Recommendation	Specific Drug Combinations
Localized Cancer or Other Terminal Condition-Related Pain	Line 1B	Morphine or fentanyl + bupivacaine
	Line 2	Hydromorphone + bupivacaine Hydromorphone or fentanyl or morphine + clonidine Morphine or hydromorphone or fentanyl + ziconotide
Diffuse Cancer or Other Terminal Condition-Related Pain	Line 1B	Morphine or hydromorphone + bupivacaine
	Line 2	Hydromorphone or morphine + clonidine Morphine or hydromorphone + ziconotide
Localized Non Cancer-Related Pain	Line 1B	Fentanyl + bupivacaine
	Line 2	Fentanyl + clonidine Hydromorphone or morphine + bupivacaine Fentanyl + bupivacaine + clonidine
Diffuse Non Cancer-Related Pain	Line 1B	Morphine or hydromorphone + bupivacaine

There are no first line (Line 1A) recommendations for combination drug therapy. All pain indications are for nociceptive or neuropathic pain. Line 3-6 recommendations not included in this table.

Table 2. *Pharmacokinetic and pharmacodynamic parameters of standard intrathecal medications in pain management.*

Drug	Lipophilic vs Hydrophilic	Onset of Action (min)	Duration of Action (hr)	Starting Dose	Maximum Dose	Mechanism of Action	Common Adverse Effects
Morphine	Hydrophilic	30-60	6-24	0.1-0.5 mg/day	15 mg/day	Agonism of mu, kappa, and gamma opioid receptors at the substantia gelatinosa in the dorsal horn of the spinal cord	Pruritus, peripheral edema sedation, respiratory depression, constipation, urinary retention, decreased sex steroids
Hydromorphone	Hydrophilic	30-60	6-24	0.02-0.5 mg/day	10 mg/day		
Fentanyl	Lipophilic	5-10	2-4	25-75 mcg/day	No known limit		
Sufentanil	Lipophilic	<10	2-6	10-20 mcg/day	No known limit		
Bupivacaine	Lipophilic	5-10	2-3	1-4 mg/day	10 mg/day	Antagonist of intracellular sodium channels, preventing depolarization	Urinary retention, paresthesias, paresis, orthostatic hypotension
Ziconotide	Hydrophilic	60-120	4-24	0.5-2.4 mcg/day	19.2 mcg/day	Reversible antagonist of voltage-sensitive calcium channels at the spinal cord dorsal horns	Dizziness, nausea, somnolence, confusion, visual disturbance, urinary retention
Clonidine	Lipophilic	25-30	0.6-1.3	40-100 mcg/day	40-600 mcg/day	Alpha 2-agonist which acts at the pre and postsynaptic neurons in the spinal cord and possibly by inhibition of proinflammatory cytokines	Sedation, hypotension, bradycardia

The additive adverse effects with polyanalgesia must be recognized to maintain appropriate safety profiles. This is evident with a heightened risk of hypotension with combination opioids and clonidine or altered mentation with opioids and ziconotide (13). Therefore, in patients with CIDT employing an opioid medication, dose titration should be judicious, especially in those patients with opioid sensitivity (1-3). On the contrary, while synergistic benefits of CIDT pharmacodynamics have yet to be clearly established, there exists evidence and rationale for certain combinations and pain syndromes that require consideration in appropriate patients that meet selection criteria (1,2,4-6). Additionally, trialing new combinations is recommended before initiating new CIDT regimens as this helps identify appropriateness, benefit, and safety concerns (13).

Specific Drug Combinations

As aforementioned, CIDT is not currently recommended as a first-line treatment or until FDA-approved monotherapy is tried, failed, or contraindicated (2017 PACC guidelines, consensus point 9) (1). The supportive evidence for CIDT use for chronic pain conditions is largely lacking and limited to small, uncontrolled studies. A primary objective of this section is to provide a robust exploration of the literature to highlight specific drug combinations utilized in the treatment of nociceptive, neuropathic, and cancer-related chronic pain. The most prevalent CIDT strategies include polyanalgesia with morphine-ziconotide (Table 3), opioid-clonidine (Table 4), and morphine-bupivacaine (Table 5).

It should be noted that baclofen, which is FDA approved for intrathecal use to treat spasticity, has also been used as part of CIDT regimens to treat patients with concomitant chronic pain and spasticity (25). Given that the evidence of combinations is further lacking and this population represents a minority of those patients with intrathecal therapy for pain, CIDT with baclofen is not discussed in this manuscript.

The majority of studies were observational in nature and had various confounding factors, such as concomitant oral medication use and a lack of standardized dosing. Future studies should aim to fill these gaps and may benefit from the inclusion of objective,

Table 3. *Combination intrathecal drug delivery strategies with Morphine (+/- other agents) and Ziconotide.*

Author, Year	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Wallace et al 2008 (26)	Morphine (2-20 mg/ day)	Ziconotide (0.60-7.2 µg/ day)	Phase II, Open-Label Multicenter Study (N=26)	- Mean improvement in VAS of 14.5% (baseline versus 5-week follow up) and was noted as early as Week 2 - Mean decrease in systemic opioid consumption of 14.3% at 5-week follow up - At termination visit following extension phase, 10 of the 17 enrolled patients reported slight to complete improvement in pain relief - Overall, CIDT found to be safe and effective	- Adverse effects included confusion, dizziness, abnormal gait, hallucinations, and anxiety; all 26 patients reported at least one mild adverse effect during titration phase, and all recovered - 6/26 patients discontinued CIDT prior to end of 5-week titration phase due to adverse effects - 2/16 patients reported serious adverse events, including cellulitis, cerebral ischemia, and stupor; however, none were reported to be due to CIDT
Webster et al 2008 (28)	Ziconotide (4.8-24.20 µg/day)	Morphine (0-2.1 mg/day)	Multicenter, open-label study (N=25)	- Patients on Ziconotide monotherapy evaluated over 4-weeks after addition of morphine; VASPI decreased by a mean of 26.3% - Median systemic opioid consumption reduced by 49.1% at week 4 (baseline of 840 mg//week) - At week 72, decrease was 61.1% - 5/24 patients remaining in the study after 4-weeks converted back to monotherapy	- All 25 patients had at least one adverse effect, including: nausea (4), peripheral edema (3), dizziness (7), pruritus (6); 88% of patients experienced these effects in the first 2-weeks - 2 patients reported serious treatment related adverse effects, including: ataxia, confusion, subdural hematoma, urinary tract infection; none were considered to be related to CIDT - 1 patient dropped out at 4 weeks given adverse effects
Dupoiron D et al 2012 (43)	Morphine (19.3 mg/ day) Ropivacaine (18.3 mg/ day) Clonidine (9.3 µg/day)	Ziconotide (3.5 µg/day)	Prospective Observational Study (n=77)	-77 patients with incurable cancer causing pain with a VAS of 6/10 or above were selected to receive intrathecal ziconotide with morphine, ropivacaine, clonidine. -Objectives were to 1) measure the incidence of ziconotide-related adverse events and 2) if slow-titration provided affected degree of pain relief -All patients experienced a significant and lasting decrease in pain intensity (by 48%), in response to intrathecal analgesic therapy that included ziconotide. -Rates of minor and moderate adverse effects were consistent with previous studies. Rates of serious adverse events were substantially lower.	-Nonrandomized, observational study -Adverse effects were recorded in 57% of patients. 7 patients experienced serious adverse effects that required discontinuation of CIDT. -Adverse events included memory alterations (20), mood disorders (19), confusion (12), visual disorders (7), vertigo (7), CPK elevation (2), speech disorders (6), nausea (23), diaphoresis (6), urinary retention (13), hypotension (9). -Due to varied doses of intrathecal morphine, ropivacaine, and clonidine, difficult to discern cause of specific adverse effects.
Puntillo F et al 2020 (33)	Morphine (2 mg/day)	Ziconotide (2.8 µg/day) Levobupiva-caine 3.8 mg/day)	Prospective Observational Study (n=60)	-60 adults with refractory chronic cancer pain were selected to receive CIDT with morphine, ziconotide, and levobupivacaine. -VASPI scores were recorded over weeks for the primary outcome. - VASPI scores had statistically significant improvement from a mean of 88 at baseline to 49 at day 2 and 44 at day 56. -The mean doses of all three drugs increased over the length of study -Demonstrated rapid and stable control of cancer-related pain	-The incidence of adverse affects ranged from 3.3 to 10%, which included dizziness (5), confusion (6), urinary retention (6), nausea (6), vomiting (3), hallucinations (2). -No patients reported leg anesthesia or weakness -In patients in which ziconotide dose had to be reduced due to adverse effects, morphine and levobupivacaine had to be increased -Limited due to single arm study, non-randomized, length of study

Table 3 (cont.). *Combination intrathecal drug delivery strategies with Morphine (+/- other agents) and Ziconotide.*

Author, Year	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Alicino I et al.,2012 (32)	Morphine (1.2 mg/day)	Ziconotide (3.54 μg/day)	Prospective Observational Study (n=20)	-20 patients with a mean visual analogue scale of pain intensity (VASPI) of 90 from disseminated cancer with bone metastasis involving the spine were selected to receive IT therapy with ziconotide and morphine -IT ziconotide was started at 2.4 μg/day and slowly titrated up. IT Morphine initial dose was calculated based on patient's previous morphine equivalent -No maximum dose limit was defined for either drug and was titrated based on analgesia and side effects -The percentage decreases reported were at 2 days (39 +/- 13), 7 days (51 +/- 12), and 28 days (62 +/- 13)..	-Four patients experienced transient adverse effects including dizziness, asthenia, confusion, and ataxia -Due to patients with a short life expectancy from cancer progression, observation was only conducted for 1 month as only 5 patients survived until the third month. -Opioids can accelerate the rate of ziconotide degradation and therefore must be an important consideration regarding frequency of pump refills. This study had weekly pump refills to ensure stable ziconotide concentrations.
Deer et al.,2009 (29)	Hydromorphone (4.6 mg/day, N=7) Morphine (5.2 mg/day, N=5) Fentanyl (990 μg/day, N=3) Sufentanil (1100 μg/day, N=1)	Ziconotide (0.61-5.7 μg/day)	Retrospective Review (N=16)	- Substantial pain relief (VAS score decrease > 4) reported in 3 patients at week 12; 4 reported mild to moderate relief; 6 reported no change in pain; 2 reported increased pain - Increase in functional capacity evident in 3 patients at week 12 as determined by Oswestry Disability Index - Addition of Ziconotide improved pain in 46.7% of patients	- 1 patient noted increased depression and pain with CIDT, resulting in discontinuation of ziconotide and resolution of symptoms - Adjunct medications included Bupivacaine, Clonidine, Baclofen - may introduce confounding factors into study
Hayek et al.,2015 (31)	Variable (Hydromorphone, Fentanyl, Bupivacaine, or combination thereof)	Ziconotide (7.6 μg/day)	Retrospective Review (Case Series, N=15)	- 4/15 patients failed CIDT trials, 11 patients proceeded to Ziconotide treatment - 4/11 patients continued ziconotide through 24 months with improved pain - Baseline NRS 8.1 changed to 6.3 at 3 months (N=9), 6.8 at 6 months (N=9), 8.0 at 12 months (N=6), 6.3 at 18 months (N=5), and 8.5 at 24 months (N=4) - Pain relief only statistically significant at 3 months, after which there was a trend towards loss of effectiveness	- 7/11 patients experienced adverse effects with Ziconotide addition, resulting in discontinuation of CIDT; these included presyncope, nausea, dyspnea, lower extremity numbness - High incidence of adverse effects with Ziconotide may limit its effectiveness as CIDT
De la calle gil et al.,2015 (35)	Morphine with bupivacaine (7.63 mg/day	Ziconotide (4.9 μg/day)	Case Series (n=8)	-Ziconotide adjunctive therapy was added to morphine if patients had >=5 on VAS after three 20% increases of morphine -Pain intensity was reduced in all patients after initiation of ziconotide within 3-5 days -Promotes successful pain control in cancer patients with severe refractory neuropathic pain.	-Ziconotide has a narrow therapeutic range, requiring careful, slow titration to avoid adverse effects -4 of the eight patients discontinued intrathecal ziconotide because of psychological/neurologic adverse events, 3 patients died for unrelated reasons, and 1 patient is still receiving treatment -Bupivacaine concentration not specified -Oral adjunctive medications varied amongst the 8 patients

Table 3 (cont.). *Combination intrathecal drug delivery strategies with Morphine (+/- other agents) and Ziconotide.*

Author, Year	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Saulino,2007 (30)	Hydromorphone (1.32 mg/day)	Ziconotide (11 μg/day)	Case Report (N=1)	- Mixed pain in SCI patient with initial VASPI of 89 prior to hydromorphone monotherapy which reduced VASPI to 7 at-level but with VASPI 82 for below-level pain - Switched to ziconotide monotherapy with improvement of below-level pain (VASPI = 4) but worsening of at-level pain (VASPI = 72) - CIDT resulted in VASPI of 12 for at-level pain and VASPI of 8 for below-level pain without significant side effects	- Previously failed hydromorphone + clonidine + bupivacaine CIDT

CIDT: combination intrathecal drug therapy; VAS: visual analog scale; NRS: numerical rating scale; VASPI: visual analog scale of pain intensity; SCI: spinal cord injury

secondary outcome measurements analyzing the quality of life and function in addition to primary outcome measurements of pain relief and adverse effects. At this time, current clinical practice is beholden largely to consensus guidelines when using CIDT for patients with refractory pain phenomena. Perhaps, at least in part due to this scarcity of evidence basis, insurance payer coverage for CIDT formulations varies extensively and relatedly, so too does widespread incorporation of these strategies in clinical practice. While the use of such combinations is off-label, it should be recognized that a vast majority of intrathecal treatment strategies are off-label, per a recent large cohort study of patients with nonmalignant pain (26).

CIDT With Morphine and Ziconotide

In 2008, Wallace et al (27) performed a multicenter open-label study exploring the benefits of CIDT with ziconotide adjunct in patients with stable dosage intrathecal morphine. This investigation followed findings of additive or synergistic analgesia in rat models and a clinical need for CIDT strategies given refractory or suboptimal pain relief in a subset of patients with morphine (28). Briefly, Wallace et al (27) found mild-modest pain improvement (VASPI decrement of 14.5% through 5 weeks) in a small cohort of patients treated with ziconotide and morphine concomitantly. Perhaps just as importantly, they found this combination to be safe with limited adverse effects in the extension phase of treatment with no reports of severe morbidity or mortality. Interestingly, also in 2008, Webster et al performed a multicenter open-label study exploring the benefits of CIDT with morphine adjunct in patients with stable dosage intrathecal ziconotide (29). They also found a comparable pain improvement (VASPI decrease of 26.3% through 4 weeks) in their small cohort, but additionally found that a near 50% enteral opioid intake reduction at 4 weeks was sustained at 56 weeks.

Unfortunately, drug dosing in the extension phases of both the Wallace et al (27) and Webster et al (29) studies was subject to physician discretion. This absence of a structured algorithm fails to provide clinical guidance for intrathecal maintenance dosing when using CIDT with morphine and ziconotide. A safe and meaningful benefit with this combination has been corroborated in the literature with mixed results (30-36). While one case series and report reported fair safety profiles and good benefit, Hayek et al (31) published a report of their experience with ziconotide adjunct indicating that 7 of 11 patients required ziconotide discontinuation for various adverse effects, with 2 of these 7 patients having improved pain thereafter (30-32). While Hayek et al's findings are confounded given that their cohort had variable preceding combinations of opioids and bupivacaine, they still warrant notable consideration given the longevity of patient follow-up (24 months).

Interplay with anesthetic-ziconotide CIDT is poorly understood but requires future exploration. However, morphine-ziconotine CIDT has been demonstrated to be relatively safe, except possibly with the addition of > 2 total agents, including anesthetics (Table 3). This combination has also been shown to be effective in yielding additive pain reduction as supported by multiple

Table 4. *Combination intrathecal drug delivery strategies with Morphine (+/- other agents) and Clonidine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Siddall et al.,2000 (39)	Morphine (0.75 mg/day)	Clonidine (50 µg/day)	Double-Blinded, Randomized Controlled Trial (N=15)	- 5/15 patients responded positively (>50% relief from baseline) to saline placebo - Morphine monotherapy reduced pain levels to 80% of baseline; clonidine monotherapy reduced pain to 83% of baseline (not statistically significant) - CIDT reduced pain level to 63% of baseline (statistically significant)	- Most common side effects after morphine included pruritus, sedation, nausea, hypotension, oxygen desaturation - Most common side effects after clonidine were hypotension, nausea, sedation, oxygen desaturation, dry mouth - Hypotension and dry mouth were approximately equivocal with CIDT compared to monotherapy, whereas oxygen desaturation and sedation were more common in morphine monotherapy - In patients who received saline placebo, 13% reported sedation or oxygen desaturations
Uhle et al.,2000 (36)	Clonidine (44 µg/day)	Morphine (0.48 mg/day, variable)	Prospective Observational Study (N=10)	- 4 patients received combination clonidine/ morphine after inadequate pain control with monotherapy alone - CIDT decreased dose and side effects of clonidine via addition of opioids	- Side effects attributed to clonidine included urinary dysfunction (1), impotence (1), and asymptomatic hypotension (1) - No statistical analyses performed given small sample size
Ackerman et al.,2003 (36)	Clonidine (75-950 µg/day)	Morphine (N=4, 0.15-15 mg/day) Hydromorphone (N=3, 200-8000 µg/day)	Retrospective Review (N=15)	- 5/15 patients had no improvement with clonidine trial and were not considered for long term therapy; 10 underwent long term treatment with clonidine - VAS decreased from 7.11 to 2.85 - 2 patients dropped out - 8/8 remaining patients were switched from monotherapy to CIDT given poor pain control or excess side effects - No patient was able to achieve adequate pain response with clonidine monotherapy, and only 4 achieved acceptable relief with CIDT	- 3/4 patients failed clonidine/ morphine CIDT (3-6 months) - 1/3 patients failed clonidine/ hydromorphone CIDT (6 months) - Adverse effects attributed to clonidine included hypotension (5), sedation (3), constipation (1), confusion (1), nausea (2), pruritus (2) - 1 patient had catheter migration that required pump removal - Drop out rate, small sample size, study design, lack of objective measures all limit reliability of data
Coombs et al.,1986 (42)	Hydromorphone (15 mg/day)	Clonidine (1.5 mg/day)	Case Report (N=1)	- 49 year old female with stage 1 uterine cervical carcinoma and chronic refractory pain. Patient wished to pursue a controlled study of intrathecal narcotics. - Patient initially received 2.4 mg/day of intrathecal hydromorphone, but had to be up titrated and then later had intrathecal clonidine added - CIDT controlled the patient's pain and was able to avoid nerve destruction surgery	- Tolerance is an obstacle with chronic intrathecal administration of narcotics - At time of clonidine initiation, patient developed hypotension requiring oral ephedrine and intramuscular vasopressin - VAS fluctuated likely due to the patient developing tolerance to hydromorphone

Table 4 (cont.). *Combination intrathecal drug delivery strategies with Morphine (+/- other agents) and Clonidine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Siddall et al.,1994 (38)	Morphine (10 mg/day)	Clonidine (17 µg/day)	Case Report (N=1)	- Pain poorly controlled with morphine monotherapy but with 50% reduction in pain with addition of clonidine	- Small size, no objective pain scales used - No adverse effects reported by patient
Bevacqua et al.,2007 (40)	Fentanyl (173 µg/day), Bupivacaine (unknown)	Clonidine (72 µg/day)	Case Report (N=1)	- Patient maintained on mixture of fentanyl, bupivacaine, and clonidine with adequate pain control but then with worsening side effects (night terrors, dry mouth) at 1 year - Symptoms improved with removal of clonidine from mixture	- Limited by small size and type of study - Intrathecal clonidine may have side effects that include delirium and hallucinations, limiting its use in both monotherapy and CIDT
Koman et al.,2012 (41)	Morphine (unknown)	Clonidine (40-66 µg/day)	Case Report (N=1)	- Patient with intractable pain on morphine monotherapy with baseline VAS between 7-10 (reported 10) - VAS decreased to 4 at week 2 after addition of clonidine and remained at this level while patient treated with morphine and clonidine	- Previously failed CIDT with Ziconotide secondary to pruritus, paresthesia, diaphoresis - Significant erectile dysfunction reported that correlated with clonidine use - Clonidine discontinued after 4 weeks secondary to adverse effects and morphine monotherapy was continued, with increase in pain score back to prior baseline

CIDT = combination intrathecal drug therapy; VAS = visual analog scale; NRS = numerical rating scale

prospective and well-designed studies. Future work should serve to clarify the appropriate timing of intrathecal adjuncts, especially in patients with stable opioid dosages. Currently, it is unclear if earlier ziconotide introduction is preferred to prevent the development of intrathecal opioid tolerance or if opioid tolerance is cumulative time-dosage dependent and later ziconotide introduction is preferred to ensure salvage and continued intrathecal drug delivery. Optimal concentrations of opioid-ziconotide compounds or admixtures should also be determined in a clinical setting as this could also play a role in long-term efficacy in CIDT.

CIDT With Morphine and Clonidine

The role of alpha-2 agonists in pain modulation dates as far back as animal models in 1904. Epidural clonidine was shown to be efficacious in clinical studies by 1984, and in a 2000 prospective observational study, Uhle et al evaluated the efficacy of clonidine CIDT (37). In their cohort of patients with radicular neuropathic pain, CIDT resulted in a 70%-100% reduction in pain (VAS scores, 6-12 months) compared to monotherapy. Ackerman et al reported similar reductions of VAS scores in their 2003 retrospective review, with a decrease in VAS from 7.11 to 2.85 after initiation of CIDT (morphine or hydromorphone) (38). However, just as importantly, they reported significant limitations with intrathecal clonidine use, including variable interpatient efficacy and decreasing effectiveness over time (mean duration of relief < 18 months).

In 1994, Siddall et al 1994 published one of the earliest cases reporting CIDT with morphine and clonidine and demonstrated a 50% reduction in pain control without any adverse effects (39). Thereafter, in 2000, Siddall et al performed a double-blinded, randomized controlled trial in a cohort of patients with spinal cord injury that bolstered the evidence for this combination's efficacy while concurrently highlighting adverse effects and variability in patient responsiveness (40). Ten of 15 patients reported significant improvements in Numeric Rating Scale (NRS) scores, but these findings may not be fully generalizable in the non-spinal cord injured population.

Although these data may be promising, smaller case reports highlight adverse effects that may limit the utility of intrathecal clonidine (Table 4) (41-43). In a case report by Bevacqua et al (2007), a patient who underwent a CIDT trial with fentanyl, bupivacaine,

Table 5. *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Huang et al.,2015 (64)	Morphine (2.36 mg/day alone; 1.23 mg/day for CIDT)	Ropivacaine (4.5-15.3 mg/day)	Double-blind randomized clinical trial (n=36)	-36 patients with terminal, intractable cancer pain were selected to either receive morphine alone (n=19) or morphine with ropivacaine (n=17). -The Numerical Rating Scale (NRS) and The Barthel Index were analyzed on days 1, 3, 7, and 15 after IT therapy initiation. -Patients receiving morphine and ropivacaine had statistically significant (P<0.05) lower NRS Scores compared to morphine alone on days 1, 3, 7, and 15 after pump implantation. -Patients with CIDT also had significantly lower postoperative morphine requirements and higher Barthel Index Scores on the 15th surgical day (P <0.05)	-Adverse effects for patients receiving morphine alone included transient urinary retention (1), nausea and vomiting (3). -Adverse effects in patients with CIDT included urinary retention (1), constipation (1), nausea and vomiting (1). -Addition of ropivacaine did not induce any dermal numbness or decreased sensation -Somnolence, sedation, infection, respiratory distress, motor dysfunction, and seizures were not observed -Long term complications were not assessed because short length of study
Reif et al.,2017 (62)	Bupivacaine (42.7 – – 47.5 mg/day)	Morphine (8.7 – 40 mg/day)	Randomized double blind cross-over trial (n=23)	-23 patients received intrathecal bupivacaine and was titrated and maintained for 4 days. Patients received IT morphine on day 2 or 4 according to the randomization protocol. -IT bupivacaine alone significantly decreased pain intensity from 3-7 to 0-1. Only 1 patient of the 15 patients that remained for the duration of the 4 day study expressed preference for morphine for pain relief. -The addition of IT morphine did not result in any significant change of pain intensity, pain relief score, or total use of bupivacaine.	-IT bupivacaine alone provided significant pain relief and therefore the addition of IT morphine did not induce increased analgesia. However, it's possible that morphine could provide increased analgesia at a lower dose of IT bupivacaine. -A trial of a lower dose of IT bupivacaine could be considered unethical as this patient's would knowingly suffer from more pain -Total length of study was 5 days and therefore limiting study of long term efficacy. -No patients withdrew due to adverse events or motor impairments. No treatment related serious adverse events were detected.
Van Dongen et al.,1999 (67)	Morphine (1.2 – 7.2 mg/day)	Bupivacaine (5-21.6 mg/day)	Randomized, double blinded study (n=20)	-20 patients with refractory cancer pain were selected randomly to be a part of 2 groups. 1 group received intrathecal morphine alone (9), while the other group received morphine + bupivacaine (11) -Combination of intrathecal morphine and bupivacaine resulted in decreased progression of intrathecal morphine dose as compared to morphine alone, indicating synergistic effect of local anesthetic. -All 20 patients in the study group experienced adequate pain relief with IT treatment from days 10 to 45	-During the study period, 5 patients from the morphine group were transferred to the morphine/bupivacaine group due to poor prognosis due to stage of illness. -Small sample size of study -Severe bupivacaine-related neurological deficits were not present in the study -Drug-induced side effects was not explored in-depth to differentiate from tumor-associated neurological complications

Table 5 (cont.). *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Chen et al.,2020 (45)	Bupivacaine (9.5 mg/day)	Morphine (4.6 mg/day) Clonidine (38.9 mg/day)	Retrospective Review and Prospective Observational Study (n=120, n=43)	-Two cohorts were analyzed for this study. -Cohort A was a retrospective review of 120 patients that underwent intrathecal drug delivery system (IDDS) placement for chronic refractory cancer pain. Bupivacaine dosing algorithm was created based on this cohort for a subsequent study on 24 patients (Cohort B). -Cohort B had an average baseline VAS of 6.5 which decreased to 2.7 at time of discharge. Oral morphine equivalents decreased from 1041 mg to 307 mg. -Higher starting doses of bupivacaine can significantly shorten the time to achieve pain control in the oncologic population and thus offering an expedited discharge for the patient. -The algorithm for starting dose of bupivacaine varied based on location of catheter tip as follows: cervical spine (5 mg/day), T1-T4 (8 mg/day), T5-8 (10 mg/day). T9-12 and lumbar spine are also started 8 mg/day to reduce the risk of adverse	-Adverse effects included urinary retention or numbness (7), post-dural puncture headaches (3) -Focused on bupivacaine in isolation. Morphine and clonidine doses varied amongst patients and were not standardized. - Length of study limited to hospitalization and patient's intrathecal pump adjustments after discharge was not accounted for.
Mercadante et al.,2007 (47)	Morphine (19.7 mg/day)	Levobupivacaine (54.4 mg/day)	Prospective observational study (n=55)	-55 patients with refractory chronic pain due to advanced cancer were selected to receive intrathecal morphine with levobupivacaine -Pain severity was measured monthly from baseline until time of death. -The mean baseline VAS was 7.98 and improved to 3.00 (discharge), 3.87 (1 month), 3.92 (3 months), 3 (6 months), and 3.92 (1 week prior to death). Number of patients varied depending on survival at different intervals. 44 patients were followed until death. -An oral-intrathecal conversion ratio of 100:1 and local anesthetics provided rapid and long-term pain control and decreased opioid consumption until death.	-Complications included mild bleeding (2), headache (4), urinary retention (6), catheter malfunction (4), unrelated death (1), and stroke (1), local infection (2), spinal compression (1). -Controlled study difficult to perform given patient complexity, and ethical considerations for pain control. -One patient received intrathecal clonidine which could contribute to side effects and/or analgesia effects.
Sjoberg et al.,1994 (49)	Morphine (5 mg/day)	Bupivacaine (50 mg/day)	Prospective Observational Study (n = 53)	-53 patients with refractory cancer pain were given a constant infusion of 0.5mg/mL plus 4.75mg/mL bupivacaine to study the clinical efficacy of a constant infusion in a 1:10 ratio. -Efficacy was estimated from VAS, daily dosages of both IT and oral opioids, gait, sleep, and daily activities. -All 53 patients obtained acceptable pain relief, with a reduction in VAS from 6-10 to 0-2. -Total opioid consumption decreased (10mg vs 120mg), sleep duration doubled, and consumption of non-opioid and sedatives also decreased.	-Intrathecal morphine side effects were not recorded for any patients (seizures, cerebral or spinal clonus) -Intrathecal bupivacaine adverse effects included late urinary retention (9 patients), paresthesia (11 patients), paresis/gait impairment (9 patients), and occasional episodes of orthostatic hypotension (1 patient) -35 of 53 patients had pain in the thoracic, lumbar, or sacral nerves distribution. -The results from this study of 1:10 (morphine:bupivacaine) are unable to be compared to previous study from the same authors of 1:1 as there were significant differences in the patient population and other confounding factors.

Table 5 (cont.). *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Sjoberg et al.,1991 (48)	Morphine (2-10 mg/day)	Bupivacaine (<30 mg/day)	Prospective Observational Study (n=52)	-52 patients were selected based on unsatisfactory pain control with extradural administration of morphine and bupivacaine, systemic opioids with intolerable side effects, short trial of intrathecal morphine alone was ineffective, and other therapeutic interventions not appropriate. -Patients first received equal concentrations of intrathecal morphine and bupivacaine, and were adjusted according to morphine or bupivacaine side effects -Patients were monitored for a range of 1-305 days (median = 23) -CIDT decreased total consumption of opioids (all routes), improved sleep, gait, and daily activities -44 of 52 patients reported significant pain relief, with improvement in 85% in VAS -IT-morphine doses were reduced in more than half of the patients when combined with IT-bupivacaine	-Adverse effects of paresthesia, paresis, gait impairment, urinary retention, anal sphincter disturbances, and orthostatic hypotension were reported with higher doses >60mg/day of IT-bupivacaine. -Doses of both IT-morphine and IT-bupivacaine were highly variable amongst individuals and must be individually titrated per patient's pain.
Rainov et al.,2001 (16)	Morphine (6.2 mg/day)	Bupivacaine (2.5 mg/day) or Clonidine (0.05 mg/day) or Midazolam (0.8 mg/day)	Prospective, open label, pilot cohort study (N=26)	- Morphine +1 agent used in 10 patients - Morphine +2 agents in 12 patients - Morphine +3 agents in 4 patients - 19 patients reported "excellent" results, 6 patients reported "sufficient" results, 1 patient had "poor" results	- No long term side effects reported - Morphine dose increased from 1.2 mg at baseline to 5.1 mg at 24 months, indicating the development of tolerance - 2 patients had hardware complications with catheter leakage or occlusion
Mironer et al.,2002 (57)	Morphine (N=19, 11.85 mg/day) Hydromorphone (N=5, 13.7 mg/day)	Bupivacaine (0, 4, 6, 8 mg/day)	Prospective Observational Study (N=24)	- Study compared IT opioid monotherapy to CIDT (opioid + varying dose of bupivacaine) in patients with mix of nociceptive/neuropathic pain - Baseline VAS score of 6.8 decreased to 6.3 at 1-month and 6.5 at 4-months - Statistically significant improvement in quality of life scores with opioid + 6mg/day bupivacaine, not seen at 8mg/day dose - No statistically significant improvement in VAS scores with CIDT compared to monotherapy	- 1 patient reported lower extremity numbness when given opioid + bupivacaine
Mercadante et al.,1994 (63)	Morphine (4.6 mg/day)	Bupivacaine (25 mg/day)	Prospective Observational Study (n=15)	15 patients with advanced cancer pain (life expectancy <2 months) who no longer had adequate pain control on oral or parenterally administered opioids were selected to receive continuous intrathecal infusion with morphine and bupivacaine -13 out of 15 intrathecal catheterizations were performed at the patient's home due to inability or refusal of hospitalization. Free flow of CSF through the catheter confirmed subarachnoid placement -13/15 (86.6%) had good pain relief (continuously <4 VAS) throughout the observation period (every 2 days until day before death), with an average length of 15.7 days.	-One case of catheter dislodgement was reported, and was controlled with a simple suture to stop the leakage. -Majority of patients experienced pain relief with little or no sympathetic or sensorimotor impairment at bupivacaine concentrations of 0.25% - 0.5%. -Efficacy of quality of life and gross motor impairments were limited in evaluation as patients were bedridden and near end of life. -Study focused on providing pain relief for end of life.

Table 5 (cont.). *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Goucke et al.,2010 (58)	Morphine (6-14 mg/day, N=5) or hydromorphone (2-4.6 mg/day, N=7)	Bupivacaine (4-21.4 mg/day)	Prospective, open label, pilot cohort study (N=12)	- Objective was to study bupivacaine stability with increasing doses in patients already receiving IT opioids chronically - Bupivacaine stability determined to be excellent between 2-7 weeks - No clinically significant changes in VAS or ODI were seen, and this was not a primary outcome measure - Caution must be exercised with high concentrations of bupivacaine to avoid neurotoxicity	- 2 patients experienced reversible motor weakness - 3 patients withdrew from the study in the first 2-weeks; 1 for worsening weakness, 1 for worsening depression, and 1 for unrelated burns - Short follow up time (60 days) is a limitation
Veizi et al.,2011 (51)	Opioids (average dose 1.83-2 mg/day, including Morphine and Hydromorphone)	Bupivacaine (6 mg/day)	Retrospective Review (N=126)	- Baseline NRS of 7.42 decreased to 5.85 in IT opioid group and 5.03 in CIDT group - Rate of increase of intrathecal opioids in monotherapy group at 12-months was 535% compared to 185% in CIDT group - Both groups illustrated a significant decrease in oral opioid consumption compared to baseline	- No major adverse effects or changes in neurologic exams were reported with CIDT
Deer et al.,2002 (55)	Morphine (8 mg/day) Hydromorphone (1.5 mg/day)	Bupivacaine (2.0-25 mg/day, average of 10mg/day)	Retrospective Review (N=109)	- CIDT patients experienced greater pain relief, consumed less opioids, had higher satisfaction, and fewer emergency room visits compared to monotherapy treatment - Baseline VAS 6.4 with opioids alone, compared to CIDT VAS score 3.2 ($p<0.05$)	- 2 patients experienced mild paresthesias after bupivacaine addition, 1 patient had peripheral edema - all dissipated with removal of bupivacaine - Other neurologic or adverse effects were attributed to primary disease (84 non-cancer patients, 25 cancer patients)
Galicia et al.,2018 (54)	Hydromorphone (mean 112.30 µg/day)	Bupivacaine (mean 6.0 mg/day)	Retrospective Review (N=62)	- 54/62 had successful intrathecal trial with CIDT - No significant differences were found in age, gender, pre-trial NRS, pre-trial MEDD, or trial dosages between those who failed or passed intrathecal trial - Baseline NRS of 8 decreased to 5.5 at 12-months and was 6.0 at 24-months with CIDT - Overall, CIDT was determined to be safe and efficacious	- 4/62 patients had servere post-dural puncture headache that resolved with epidural blood patch - Retrospective design with incomplete data limited some statistical analyses
Ade et al.,2020 (52)	Bupivacaine (11.0-13.4 mg/day) Fentanyl (18.4-24.7 µg/day)	Bupivacaine (10.3-10.8 mg/day) Hydromorphone(151.9-345.72 µg/day)	Retrospective Comparative Analysis (N=58)	- Both CIDT groups had similar reduction in pain at 2-year follow up - Bupivacaine + fentanyl group had lower rate of intrathecal opioid dose escalation - Study found no intrathecal granuloma formation with lower doses of opioids, which may be a benefit of CIDT	- No major adverse effects or changes in neurologic exams were reported with CIDT
Hayek et al.,2016 (50)	Hydromorphone (79-487 µg/day)	Bupivacaine (5.8-12.6 mg/day)	Retrospective Review (N=57)	- Baseline NRS of 8.4 decreased to 4.9 at 6-months (only statistically significant group), 5.2 at 12-months, 4.3 at 24-months - Average oral opioid doses in morphine equivalents decreased from 56 mg/day to 15 mg/day at 24-months - CIDT was effective for chronic pain	- 3 patients had migration of catheter outside intrathecal space, 3 patients had puncture of catheter when evaluated by contrast studies, 3 patients had catheter kinks - Superficial wound dehiscence occurred in 4 patients, all were successfully revised - 4 patients had postoperative wound infections requiring removal of pump - 1 patient developed pump infection with refill - CIDT related complications included lower extremity edema (2 patients)

Table 5 (cont.). *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Van Dongen et al.,1993 (68)	Morphine (8 mg/day)	Bupivacaine (31 mg/day)	Retrospective Review (n=51)	-51 patients with refractory cancer pain were treated with intrathecal morphine, 17 of which received a morphine/bupivacaine mixture due to inadequate pain control with morphine alone. -After addition of IT bupivacaine, 10/17 patients had good pain relief, 4 had moderate pain relief, and 3 had persistent inadequate pain control. -Effectiveness of therapies was measured by verbal expression from parents and need of additional analgesics.	-Bupivacaine-induced side effects were absent below a daily dose of 30mg -Common side effects or complications included nausea (11), disconnection of catheter (9), urinary retention (5), and headache (5). -No serious complication, neurologic sequelae, or meningitis occurred. -Concomitant oral analgesic medications were not controlled -Routine determination of the VAS could not be analyzed due to retrospective nature of this study. -Duration of treatment differed, with the morphine group having a mean of 61 days vs. 112 days for morphine/bupivacaine
Raffaeli et al.,2008 (53)	Morphine (1.03 mg/day)	Bupivacaine (1.15 mg/day)	Retrospective Review (N=32)	- Evaluated geriatric patients with mix of nociceptive/neuropathic pain - If pain uncontrolled with morphine monotherapy (dose = 0.5mg/day), bupivacaine added - 21/32 patients benefited from CIDT - At 3-month follow up, average VAS score reduced from 8.09 to 3.21 - At 48-month follow up, average VAS score was 1.68	- 2 patients (both removed from study) had complications related to implantation procedure itself: septic meningitis (1), abdominal fluid collection (1) - Complications seen in 16/32 patients: constipation (34.4%), drowsiness (21.9%), nausea (21.9%), urinary retention (18.8%) - No patient had removal of implanted device
Krames et al.,1993 (56)	Morphine or Hydromorphone (0.065-18 mg/day of morphine equivalents)	Bupivacaine (3-4.5 mg/day)	Retrospective Review (N=16)	- 13/16 patients underwent CIDT with bupivacaine - CIDT improved analgesia in 2/3 patients with nociceptive pain and 8/10 patients with pure or mixed neuropathic pain - CIDT increase analgesia and decrease opioid side effects in 10/13 CIDT patients	- Adverse effects included catheter kink (1), migration of cether level (1), temporary radiculitis (1), cerebrospinal fluid hygroma (1), pump hybrid failure requiring replacement (1), pump site seroma (1), postspinal headache (5) - CIDT adverse effects included arthralgia and amenorrhea (3), diarrhea (1), lower extremity edema (1) - No statistical analysis or objective measures done given small sample size, per authors
Wagemans et al.1997 (69)	Morphine	Bupivacaine	Retrospective Review (n=14)	-Post-mortem neurohistopathological findings of 10 patients with refractory cancer pain who received intrathecal treatment and 4 control patients were analyzed. -The catheter tract, dura, meninges, spinal cord, and nerve roots were analyzed. -Patients were treated with IT morphine/NaCl or IT morphine/bupivacaine -Patient's received treatment for a total of 8-452 days. -Cumulative IT morphine received ranged from 22-3895mg and IT bupivacaine 0-3250mg -No macroscopic abnormalities were noted on examination. Microscopically, foreign body giant cells noted on 2 patients.	-The discrete and limited neurohistopatholigical findings on post-mortem examination suggests that intrathecal delivery of morphine with or without bupivacaine does not cause significant neurotoxic effects

Table 5 (cont.). *Combination intrathecal drug delivery strategies with Opioids (+/- other agents) and Bupivacaine.*

Author (Year)	Primary Drug (average or final dose)	Adjunct Drug (average or final dose)	Study Design (Sample Size)	Key Findings	Complications/Limitations
Mastenbroek et al.,2016 (46)	Morphine (19.6 mg/day)	Bupivacaine (13.7 mg/day) Clonidine (287.5 mcg/day)	Retrospective Review (n=9)	-9 patients suffering from severe, refractory cancer pain were included in the study. -Patient received IT morphine, bupivacaine, and clonidine based on patient's previous oral dosing. -Effectiveness of CIDT was measured using the NRS prior to initiation, immediately after initiation, at hospital discharge, and last obtained scores prior to death. -All patients were free of pain after initiation of intrathecal therapy. Mean NRS was 8.2 prior to initiation and subsequently 2.4 just after initiation. -In the last few days prior to death, half the patients were pain free.	-There was a slight increase in NRS (4.1) at 11 week follow up, possibly due to tolerance vs progression of disease. -No severe adverse events recorded during review (hypotension or respiratory depression) -Mild adverse effects documented included mild hypotension (3), which corrected with clonidine dose adjustment, and lower extremity weakness (3) which corrected after bupivacaine dose adjustment.
Guo et al.,2019 (65)	Morphine	Ropivacaine	Case series (n=3)	-Spinal myoclonus is described as a sudden, brief, shock-like muscle contraction originating from the CNS. -Three patients developed myoclonus after dose adjustments in IT opioid delivery -Patients were treated effectively with reduction in dose/infusion rate, switching from IT therapy to systemic administration, or correcting infusion/bolus parameter mistakes -Myoclonus occurred when daily doses of morphine reached 38.9mg, 45mg, and 48mg and ropivacaine daily doses of 22.5mg, and 24mg.	-Spinal myoclonus is an adverse effect that should be quickly addressed. -Dosing of intrathecal drugs should not exceed maximum daily doses by guidelines and infusion rates should be slowly titrated to prevent this rare, but known complication. -All three patients passed away within the next 3 months from multiorgan failure or respiratory failure, unlikely to be related to myoclonus event as no patient experienced repeat episodes.
Talu et al.,2005 (59)	Morphine (2 mg/day)	Bupivacaine (1 mg/day)	Case Report (N=1)	- CIDT effective in treatment of phantom limb pain uncontrolled by oral medications	- No adverse effects reported

VAS = visual analog scale; ODI = Oswestry Disability Index; IT = intrathecal; CIDT = combination intrathecal drug therapy; NRS = numerical rating scale; MEDD = morphine milligram equivalents; CSF = cerebrospinal fluid; CNS = central nervous system; IDDS = implantable drug delivery system

and clonidine reported significant side effects, including depression, night terrors, and insomnia, that were associated with clonidine; these symptoms all resolved after discontinuation of clonidine (41). Similarly, a case report by Koman et al illustrated a correlation between clonidine, reduction in Visual Analog Scale (VAS) scores, and erectile dysfunction, resulting in discontinuation of clonidine (42). It is evident that further studies are needed to elucidate the role of clonidine CIDT, particularly with respect to patient selection. The efficacy of clonidine likely correlates with its CSF concentration (Siddal et al 2000), and clonidine CIDT role in spinal cord injury at-level neuropathic pain as well as catheter placement warrants exploration (40).

With respect to cancer-related pain, clonidine has been studied in combination with multiple other agents (morphine, bupivacaine, ketamine, naloxone) in cases of severe, refractory pain (44-47). Clonidine likely has a supporting role in extreme cancer pain, but as Mastenbroek et al and Coombs et al illustrated, effective clonidine dosing requires tedious titration to appropriately achieve meaningful benefit and avoid adverse effects (43,47).

CIDT With Opioids and Bupivacaine

With the exception of ziconotide, only intrathecal opioids are typically indicated as first-line treatment for nociceptive or neuropathic pain (Table 2). While the initiation of opioid monotherapy is efficacious in reducing pain scores and enteral opioid requirements, long-term opioid monotherapy can be challenging to sustain, given known dose escalation requirements. Mercadante et al previously

demonstrated that dose escalation of opioid monotherapy increases in a near linear fashion in the nonmalignant population relative to the cancer population, presumably due to reduced lifespans in persons with cancer (48). Unfortunately, intrathecal opioid escalation is not a sustainable long-term solution given the risks for pharmacologic tolerance and adverse effects such as sedation, constipation, respiratory depression, and catheter tip granuloma formation.

Sentinel work by Sjoberg et al found that CIDT with morphine and adjunct bupivacaine reduced opioid dose escalation requirements in a cohort with refractory cancer pain (49,50). Thereafter, Hayek et al and Veizi et al were able to show that these benefits were not specific to morphine by demonstrating that patients with adjunct bupivacaine were able to maintain appropriate analgesia with hydromorphone (51,52). Ade et al (53) similarly showed that fentanyl escalation was mitigated with bupivacaine. Additionally, these studies were conducted in patients with chronic nonmalignant pain. These findings helped not only establish the necessity of intrathecal adjuncts to address opioid escalation but also helped usher a new understanding of CIDT as a means to target multiple pain receptors and mechanisms to optimize pain reduction. Therefore, in patients without terminal illnesses, cancer or otherwise, earlier introduction of CIDT strategies was thought to be imperative in mitigating eventual intrathecal opioid dose escalation to unsafe dosages.

Rainov et al (16) prospectively explored the utility of CIDT with morphine-bupivacaine in patients with chronic back and leg pain. Although their results may have been confounded by the use of multiple drug combinations (clonidine, midazolam, multi-drug intrathecal regimens), the authors' findings further supported the safe and effective use of CIDT with morphine and bupivacaine in patients with chronic nonmalignant pain. These results were further corroborated in 2008 by Raffaeli et al (54) who demonstrated improved mixed pain control with CIDT with morphine and bupivacaine compared to monotherapy in geriatric patients (VAS reduced from 8.09 to 3.21 at 3-month follow up) with sustainable analgesia (up to 48 months) . Bupivacaine with hydromorphone has also been evaluated in 2 more recent retrospective reviews, which reported similar findings of CIDT effectively decreasing baseline NRS scores (up to 24 months) (51,55). Hayek et al (51) additionally found that this combination simultaneously decreased daily morphine equivalents up to 24 months.

However, a number of studies reported variable efficacy of CIDT of bupivacaine and opioids in decreasing VAS. Deer et al (56) and Krames (57) conducted retrospective studies which illustrated greater pain relief, consumption of less opioids, increased patient satisfaction, and decreased opioid-related side effects. More recently, Ade et al (53) also retrospectively found that CIDT with fentanyl or hydromorphone individually with bupivacaine yielded comparable analgesia benefits. On the contrary, Mironer et al (58) conducted a prospective observational study and found no statistically significant improvement in VAS scores of CIDT compared to monotherapy. Moreover, neurotoxicity associated with reversible motor weakness was reported at high concentrations of bupivacaine and, therefore, should be avoided. Of note, these studies did not all make clear distinctions in the type of opioid administered between morphine or hydromorphone (Table 5) (16,48-60). Future studies should explore the optimal ratio between opioid and bupivacaine in terms of efficacy and anesthetic side effect profile.

In the oncologic population, CIDT offers patients with terminal or refractory cancer-related chronic pain an option for achieving analgesia while limiting intolerable side effects. With increasing cancer survivorship, treatment of cancer-related pain has shifted from palliative, short-term options to long-term management of chronic pain (61). Precision catheter placement for this population based on primary or metastatic lesions can provide increased pain relief. Chen et al (46) conducted a 2-cohort study to analyze the use of a fixed intrathecal bupivacaine infusion at various catheter tip locations. The catheter tip was placed at the spinal level of most severe pain, with intrathecal bupivacaine providing local analgesia at that level and concomitant morphine to provide more diffuse analgesia. Studies in animal models have shown that intrathecal bupivacaine concentrations decrease exponentially with increased distance from catheter tip location (62). This makes CIDT with opioids and local anesthetic, along with precision catheter placement, a viable option for addressing pain related to site-specific cancers. The combination of local anesthetic and opioids can achieve adequate analgesia quickly, minimize opioids and associated side effects, and allow patients to return home or to their anti-cancer therapy regimen (Table 5) (61-71).

Safety Profiles

The overall safety profile associated with CIDT may be decreased given the risk for compounded adverse

effects with polyanalgesia. While these adverse effects may be largely mitigated by effective dose reduction, appropriately identifying the implicated agent and correctly updating the CIDT dosing to maintain analgesia can be challenging in certain scenarios. Because most patients are escalated to CIDT, removing the adjunct medications will usually eliminate any new side effects. However, when patients are started on CIDT from the beginning or switched to new CIDT regimens wholly, it may be more difficult to discern which agent may be responsible for producing certain adverse effects, especially with the use of agents that share similar adverse effect profiles i.e., use of opioids and bupivacaine both of which can cause urinary retention (Table 2). In such scenarios, independently isolating intrathecal agents is necessary to implicate the responsible agent correctly.

Additionally, the mode of intrathecal delivery (simple continuous, intermittent bolus, or complex dosing) with CIDT regimens must be carefully appreciated as adverse effects can present differently for each mode. This phenomenon is especially recognized with the use of CIDT with bupivacaine, wherein rapid bolus delivery can produce numbness, which fails to manifest with the same bupivacaine dose administered via continuous fashion. Practitioners should maintain a particularly low threshold of suspicion for adverse effects in patients with CIDT such that safety profiles associated with this therapy can be favorably maintained.

Catheter Tip Granuloma Formation

Despite having an overall reported incidence of less than 3%, catheter tip granulomas (CTGs) are especially feared given that they can lead to a host of severe complications ranging from catheter occlusion to myelopathy secondary to mass effect (72,73). While conventionally associated with morphine and hydromorphone, CTGs have also been associated with other medications, including sufentanil, fentanyl, clonidine, and bupivacaine (72). Notably, ziconotide has not been associated with CTG formation (72,74). While the etiologies of CTG formation are manifold, main risk factors include opioid use with a high total dose or concentration, middle thoracic catheter placement, and prior spinal surgery (72,75). In fact, Duarte et al (76) demonstrated a direct correlation between the formation of a CTG and morphine dose and concentration, indicating the highest risk populations would be long-term patients escalated to a high dose or new patients requiring a high drug dose or concentration. With regards to CIDT, some animal studies observed that polyanalgesia with morphine and clonidine might prevent CTG formation (77). However, these findings have not been clearly established in the clinical setting, given reports of CTG formation with morphine and clonidine in the current literature (78). As discussed earlier, adjunct bupivacaine has been shown to reduce morphine escalation (49,50). Consequently, although no study has directly explored CIDT risk with morphine and bupivacaine, the addition of bupivacaine may reduce CTG risk in patients with (or at high risk for eventual) high morphine dosages.

Compounded Adverse Effects

Along with CTGs, opioids such as morphine carry a significant risk for adverse central nervous system effects, including sedation and respiratory depression. Respiratory depression is a well-known, dose-dependent adverse effect typically seen as a delayed reaction 6-12 hours after administration that may persist for up to 24 hours (79). While its incidence is rare, it is an important clinical consideration that was linked to an increased mortality risk in patients receiving intrathecal morphine (80). Interestingly, there is currently no data exploring how various CIDT may affect respiratory depression. However, given its dose-dependent relationship with opioid use, CIDT strategies, such as morphine and bupivacaine may allow reducing opioid dosage, which could decrease the overall risk of respiratory depression. In addition, judicious consideration is required when using 2 or more agents known to cause respiratory depression, if higher doses are warranted, and/or if pulmonary reserve is compromised. This is especially true with CIDT with multiple opioids (i.e., fentanyl with sufentanil, morphine with hydromorphone) which is likely associated with compounded and unsafe risks for respiratory depression. Not only do these combinations lack any substantial evidence basis, but also are not recommended for use by the recent 2017 PACC guidelines. Because the other systemic effects of opioids, such as nausea, vomiting, constipation, or urinary retention, occur due to peripheral redistribution and metabolism into active metabolites, drug metabolism and clearance must be reevaluated when treating those with liver or kidney insufficiency or when combining treatment with another drug of similar side effect profile (24).

Clonidine, an alpha-2 agonist, is well known for causing hypotension at lower doses and potential rebound hypertension at higher doses when given intrathecally (38). When used as monotherapy for chronic pain relief, doses tend to be higher, leading to more side effects. Interestingly, the side effect profile with

morphine and clonidine remains the same despite the lower concentrations of each individual drug needed for equal analgesia (39). In fact, it is possible that combination use with opioids could increase the risk for this adverse effect due to opioid propensity to precipitate bradycardia and vasodilation, leading to direct side effects of hypotension (81), as well as an inability to compensate with reflex tachycardia. Patients on CIDT with morphine and clonidine should be slowly titrated to analgesic doses in order to avoid symptomatic hypotension.

Lastly, the risk of withdrawal must always be recognized in patients with CIDT should intrathecal therapy be intentionally or unexpectedly disrupted, as possible with CTG formation. Of particular importance is baclofen withdrawal, which can prove lethal if not corrected appropriately and in a timely fashion (82). Clonidine withdrawal can also prove harmful as it can result in severe hypertensive crisis due to abruptly halted alpha receptor stimulation (82). On the other hand, ziconotide and bupivacaine have no observed withdrawal or rebound effects (83). Given these risks for withdrawal, especially significant morbidity with clonidine or opioid or even possible mortality with baclofen, measures to correct withdrawal must be timely and appropriate to prevent untoward outcomes. These measures might include intrathecal monotherapy in the short term and/or systemic correction given that CIDT compounding may take time.

Challenges With Pharmacologic Dosing

Compared with intrathecal opioid therapy, there have been no reports of death, granuloma formation, or permanent adverse effects with ziconotide (74). Additionally, it has been evidenced by high level studies to be effective for both malignant and nonmalignant pain conditions. While pain reduction with intrathecal ziconotide has been proven, dose titration can be challenging given the risk for neuropsychiatric manifestations. Pharmacodynamically, ziconotide is also known to have a ceiling effect for its analgesic properties (84). Therefore, although ziconotide is recommended as first-line monotherapy, planning CIDT with ziconotide, typically with an opioid, is recommended as a second or third-line option. However, ziconotide's drug stability decreases drastically when mixed together with opioids (86). In fact, stability is estimated to decrease from approximately 3 months to 15 days (24). While high doses of morphine are the greatest destabilizer, other medications including other opioids (hydromorphone, fentanyl, and sufentanil), baclofen, and bupivacaine also decrease shelf-life and activity (86). For this reason, it is important to extensively research the stability of drug admixtures, especially ziconotide, before beginning therapy. But it should be noted that there currently exists little to no evidence implicating CIDT with morphine, bupivacaine, and clonidine in drug destabilization. Goucke et al (59) conducted a prospective observational study of bupivacaine-opioid mixtures and found the stability to be excellent for periods between 2 and 7 weeks.

In addition to medication stability, compounds must be mixed together correctly to prevent the risk of infection and incorrect dosage. This task is surprisingly challenging with limited studies detailing the full process, in addition to an obvious lack of US Food and Drug Administration guidelines. According to the United States Pharmacopeia (USP), compounded sterile preparation will fall under low, medium, or high risk depending on the environment and methods by which it is prepared. The many steps required also open this process up to potentially more human errors in dosing and preparation. It should also be noted that most local pharmacies and many hospital-based pharmacies are likely ill-equipped to safely and appropriately compound CIDT regimens. Therefore, it is essential to utilize an experienced compounding pharmacy with the appropriate experience, personnel, equipment, and compliance with American Society of Health-System Pharmacists regulations for medication compounding to ensure quality and safety for CIDT formulations (24).

Conclusion

CIDT strategies for pain management are recommended by expert consensus guidelines, typically if monotherapy dose escalation or medication alternation is deemed untenable or unfeasible. Unfortunately, the majority of the supportive evidence basis for the use of these strategies and specific drug combinations is limited to small, uncontrolled, and observational studies, many of which have various confounding factors, including a lack of standardized dosing. We report and characterize several CIDT strategies and polyanalgesia combinations along with their reported analgesic benefit. The most evidenced CIDT strategies include morphine-ziconotide, opioid-clonidine, and morphine-bupivacaine. In addition to pain relief, polyanalgesia with morphine-bupivacaine has also been extensively evidenced to decrease early opioid escalation requirements. The appropriate use of these strategies may be limited by increased or compounded risk of adverse

effects, both of which are highly patient and scenario dependent. Therefore, practitioners should maintain a particularly low threshold of suspicion for adverse effects in patients with CIDT such that safety profiles associated with this therapy can be favorably maintained.

References

1. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on intrathecal drug infusion systems best practices and guidelines. *Neuromodulation* 2017; 20:96-132.
2. Prager J, Deer T, Levy R, et al. Best practices for intrathecal drug delivery for pain. *Neuromodulation* 2014; 17:354-372.
3. Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. *Pain Med* 2016; 17:2404-2421.
4. Abd-Elsayed AA, Karri J, Michael A, et al. Intrathecal drug delivery for chronic pain syndromes: A review of considerations in practice management. *Pain Phys* 2020; 23:E591-E617.
5. Deer TR, Abd-Elsayed A, Falowski S, et al. Practice choices in targeted intrathecal drug delivery: An online survey conducted by the Polyanalgesic Consensus Committee [published online ahead of print, 2020 Dec 23]. *Neuromodulation* 2020; 10.1111/ner.13335.
6. Duarte R, Raphael J, Eldabe S. Intrathecal drug delivery for the management of pain and spasticity in adults: An executive summary of the British Pain Society's recommendations for best clinical practice. *Br J Pain* 2016; 10:67-69.
7. Raphael JH, Southall JL, Gnanadurai TV, Treharne GJ, Kitas GD. Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain. *BMC Musculoskelet Disord* 2002; 3:1-8.
8. Raphael JH, Southall JL, Gnanadurai TV, Treharne GJ, Kitas GD. Multiple lead spinal cord stimulation for chronic mechanical low back pain: A comparative study with intrathecal opioid drug delivery. *Neuromodulation* 2004; 7:260-266.
9. Atli A, Theodore BR, Turk DC, Loeser JD. Intrathecal opioid therapy for chronic nonmalignant pain: A retrospective cohort study with 3-year follow-up. *Pain Med* 2010; 11:1010-1016.
10. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* 2015(6).
11. Peng PW, Fedoroff I, Jacques L, Kumar K. Survey of the practice of spinal cord stimulators and intrathecal analgesic delivery implants for management of pain in Canada. *Pain Res Manag* 2007; 12:281-285.
12. Hayek SM, Hanes MC. Intrathecal therapy for chronic pain: Current trends and future needs. *Curr Pain Headache Rep* 2014; 18:388.
13. Deer T, Winkelmüller W, Erdine S, Bedder M, Burchiel K. Intrathecal therapy for cancer and nonmalignant pain: Patient selection and patient management. *Neuromodulation* 1999; 2:55-66.
14. Jain S, Malinowski M, Chopra P, Varshney V, Deer TR. Intrathecal drug delivery for pain management: Recent advances and future developments. *Expert Opin Drug Deliv* 2019; 16:815-822.
15. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002; 20:4040-4049.
16. Rainov NG, Heidecke V, Burkert W. Long-term intrathecal infusion of drug combinations for chronic back and leg pain. *J Pain Symptom Manage* 2001; 22:862-871.
17. Rijn MA va., Munts AG, Marinus J, et al. Intrathecal baclofen for dystonia of complex regional pain syndrome. *Pain* 2009; 143:41-47.
18. Hsu Y, Hettiarachchi HM, Zhu DC, Linninger AA. The frequency and magnitude of cerebrospinal fluid pulsations influence intrathecal drug distribution: Key factors for interpatient variability. *Anesth Analg* 2012; 115:386-394.
19. Lawrence JJ, Coenen W, Sanchez AL, et al. On the dispersion of a drug delivered intrathecally in the spinal canal. *J Fluid Mech* 2019; 861:679-720.
20. Tangen KM, Leval R, Mehta AI, Linninger AA. Computational and in vitro experimental investigation of intrathecal drug distribution: parametric study of the effect of injection volume, cerebrospinal fluid pulsatility, and drug uptake. *Anesth Analg* 2017; 124:1686-1696.
21. Pope JE, Deer TR, Amirdelfan K, McRoberts WP, Azeem N. The pharmacology of spinal opioids and ziconotide for the treatment of non-cancer pain. *Curr Neuropharm* 2017; 15:206-216.
22. McRoberts PW, Pope JE, Apostol C. Reinstituting the bolus - new reasoning for an existing technique. *Pain Physician* 2017; 20:E601-E603.
23. Hawthorn J, Redmond K. Physiology of pain. In: Hawthorn J, Redmond K. *Pain: Causes and Management*. 1st ed. John Wiley and Sons; 1998. pp. 7-15.
24. Shah S, Staats PS, Diwan S. Pharmacological agents and compounding of intrathecal drugs. In: Buvanendran A, Diwan S, Deer T, eds. *Intrathecal Drug Delivery for Pain and Spasticity*. 1st ed. Saunders; 2011. pp. 14-24.
25. Saulino M. Simultaneous treatment of intractable pain and spasticity: Observations of combined intrathecal baclofen-morphine therapy over a 10-year clinical experience. *Eur J Phys Med Rehab* 2011; 48:39-45.
26. Schultz DM, Abd-Elsayed A, Calodney A, Stromberg K, Weaver T, Spencer RJ. Targeted drug delivery for chronic nonmalignant pain: Longitudinal data from the product surveillance registry. *Neuromodulation* 2021; 10.1111/ner.13353.
27. Wallace MS, Kosek PS, Staats P, Fisher R, Schultz DM, Leong M. Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: Addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. *Pain Med* 2008; 9:271-281.

27. Wang YX, Gao D, Pettus M, Phillips C, Bowersox SS. Interactions of intrathecally administered ziconotide, a selective blocker of neuronal N-type voltage-sensitive calcium channels, with morphine on nociception in rats. *Pain* 2000; 84:271-281.
28. Webster LR, Fakata KL, Charapata S, Fisher R, MineHart M. Open-label, multicenter study of combined intrathecal morphine and ziconotide: addition of morphine in patients receiving ziconotide for severe chronic pain. *Pain Med* 2008; 9:282-290.
29. Deer TR, Kim C, Bowman R, Tolentino D, Stewart C, Tolentino W. Intrathecal ziconotide and opioid combination therapy for noncancer pain: An observational study. *Pain Phys* 2009; 12:E291-E296.
30. Saulino M. Successful reduction of neuropathic pain associated with spinal cord injury via of a combination of intrathecal hydromorphone and ziconotide: A case report. *Spinal Cord* 2007; 45:749-752.
31. Hayek SM, Hanes MC, Wang C, Veizi IE. Ziconotide combination intrathecal therapy for noncancer pain is limited secondary to delayed adverse effects: A case series with a 24-month follow-up. *Neuromodulation* 2015; 18:397-403.
32. Alicino I, Giglio M, Manca F, Bruno F, Puntillo F. Intrathecal combination of ziconotide and morphine for refractory cancer pain: A rapidly acting and effective choice. *Pain* 2012; 153:245-249.
33. Puntillo F, Giglio M, Preziosa A, et al. Triple intrathecal combination therapy for end-stage cancer-related refractory pain: A prospective observational study with two-month follow-up. *Pain Ther* 2020; 9:783-792.
34. Dupoiron D, Bore F, Lefebvre-Kuntz D, et al. Ziconotide adverse events in patients with cancer pain: A multicenter observational study of a slow titration, multidrug protocol. *Pain Physician* 2012; 15:395-403.
35. de la Calle Gil AB, Peña Vergara I, Cormane Bornacelly MA, Pajuelo Gallego A. Intrathecal ziconotide and morphine for pain relief: A case series of eight patients with refractory cancer pain, including five cases of neuropathic pain. *Neurol Ther* 2015; 4:159-168.
36. Uhle EI, Becker R, Gatscher S, Bertalanffy H. Continuous intrathecal clonidine administration for the treatment of neuropathic pain. *Stereotact Funct Neurosurg* 2000; 75:167-175.
37. Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symp Manag* 2003; 26:668-677.
38. Siddall PJ, Gray M, Rutkowski S, Cousins MJ. Intrathecal morphine and clonidine in the management of spinal cord injury pain: A case report. *Pain* 1994; 59:147-148.
39. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesth Analg* 2000; 91:1493-1498.
40. Bevacqua BK, Fattouh M, Backonja M. Depression, night terrors, and insomnia associated with long-term intrathecal clonidine therapy. *Pain Pract* 2007; 7:36-38.
41. Koman G, Alfieri A, Rachingter J, Strauss C, Scheller C. Erectile dysfunction as rare side effect in the simultaneous intrathecal application of morphine and clonidine. *Pain Physician* 2012; 15:E523-E526.
42. Coombs DW, Saunders RL, Fratkin JD, Jensen LE, Murphy CA. Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. *J Neurosurg* 1986; 64:890-894.
43. Dupoiron D, Bore F, Lefebvre-Kuntz D, et al. Ziconotide adverse events in patients with cancer pain: A multicenter observational study of a slow titration, multidrug protocol. *Pain Physician* 2012; 15:395-403.
44. Abdolmohammadi S, Hétu PO, Néron A, Blaise G. Efficacy of an intrathecal multidrug infusion for pain control in older adults and in end-stage malignancies: A report of three cases. *Pain Res Manag* 2015; 20:118-22.
45. Chen GH, Spiegel MA, Magram YC, et al. Evaluation of fixed intrathecal bupivacaine infusion doses in the oncologic population. *Neuromodulation* 2020; 23:984-990.
46. Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. *Scand J Pain* 2017; 14:39-43.
47. Mercadante S, Intravaia G, Villari P, et al. Intrathecal treatment in cancer patients unresponsive to multiple trials of systemic opioids. *Clin J Pain* 2007; 23:793-798.
48. Sjöberg M, Appelgren L, Einarsson S, et al. Long-term intrathecal morphine and bupivacaine in "refractory" cancer pain. I. Results from the first series of 52 patients. *Acta Anaesthesiol Scand* 1991; 35:30-43.
49. Sjöberg M, Nitescu P, Appelgren L, Curelaru I. Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Results from a morphine:bupivacaine dose regimen of 0.5:4.75 mg/ml. *Anesthesiology* 1994; 80:284-297.
50. Hayek SM, Veizi E, Hanes M. Intrathecal hydromorphone and bupivacaine combination therapy for post-laminectomy syndrome optimized with patient-activated bolus device. *Pain Med* 2016; 17:561-571.
51. Veizi IE, Hayek SM, Narouze S, Pope JE, Mekhail N. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. *Pain Med* 2011; 12:1481-1489.
52. Ade T, Roh J, Sharma G, et al. Comparative effectiveness of targeted intrathecal drug delivery using a combination of bupivacaine with either low-dose fentanyl or hydromorphone in chronic back pain patients with lumbar postlaminectomy syndrome. *Pain Med* 2020; 21:1921-1928.
53. Raffaeli W, Righetti D, Caminiti A, et al. Implantable intrathecal pumps for the treatment of noncancer chronic pain in elderly population: Drug dose and clinical efficacy. *Neuromodulation* 2008; 11:33-39.
54. Galica RJ, Hayek SM, Veizi E, et al. Intrathecal trialing of continuous infusion combination therapy with hydromorphone and bupivacaine in failed back surgery patients. *Neuromodulation* 2018; 21:648-654.
55. Deer TR, Caraway DL, Kim CK, Dempsey CD, Stewart CD, McNeil KF. Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine. *Spine J* 2002; 2:274-278.
56. Krames ES, Lanning RM. Intrathecal infusional analgesia for nonmalignant pain: Analgesic efficacy of intrathecal opioid with or without bupivacaine. *J Pain Symp Manag* 1993; 8:539-548.
57. Mironer YE, Haasis JC, Chapple I, Brown C, Satterthwaite JR. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: A double blind, randomized, crossover, multicenter study by the National

Forum of Independent Pain Clinicians (NFIPC). *Neuromodulation* 2002; 5:208-213.

58. Goucke CR, Dusci LJ, Van Leeuwen S, Fairclough D, Ilett KF. Stability and tolerability of high concentrations of intrathecal bupivacaine and opioid mixtures in chronic noncancer pain: An open-label pilot study. *Pain Med* 2010; 11:1612-1618.
59. Talu GK, Erdine S. Intrathecal morphine and bupivacaine for phantom limb pain: A case report. *Pain Pract* 2005; 5:55-57.
60. Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. *Pain Med* 2016; 17:2404-2421.
61. Flack SH, Bernards CM. Cerebrospinal fluid and spinal cord distribution of hyperbaric bupivacaine and baclofen during slow intrathecal infusion in pigs. *Anesthesiology* 2010; 112:165-173.
62. Reif I, Wincent A, Stiller CO. Intrathecal analgesia by bupivacaine is not enhanced by coadministration of morphine in patients with severe cancer-related pain: A randomized double-blind cross-over study. *Int J Clin Pharmacol Ther* 2017; 55:525.
63. Mercadante S. Intrathecal morphine and bupivacaine in advanced cancer pain patients implanted at home. *J Pain Symp Manag* 1994; 9:201-207.
64. Huang Y, Li X, Zhu T, Lin J, Tao G. Efficacy and safety of ropivacaine addition to intrathecal morphine for pain management in intractable cancer. *Mediators Inflamm* 2015; 2015:439014.
65. Guo X, Li Y, Yang Y, et al. Intrathecal morphine combined with ropivacaine induces spinal myoclonus in cancer patients with an implanted intrathecal drug delivery system: Three case reports. *Medicine* 2019; 98(18).
66. Lauretti GR, Rizzo CC, Mattos AL, Rodrigues SW. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. *Br J Cancer* 2013; 108:259-264.
67. van Dongen RT, Crul BJ, van Egmond J. Intrathecal coadministration of bupivacaine diminshes morphine dose progression during long-term intrathecal infusion in cancer patients. *Clin J Pain* 1999; 15:166-172.
68. Van Dongen RT, Crul BJ, De Bock M. Long-term intrathecal infusion of morphine and morphine/bupivacaine mixtures in the treatment of cancer pain: a retrospective analysis of 51 cases. *Pain* 1993; 55:119-123.
69. Wagemans MF, van der Valk P, Spoelder EM, Zuurmond WW, de Lange JJ. Neurohistopathological findings after continuous intrathecal administration of morphine or a morphine/bupivacaine mixture in cancer pain patients. *Acta Anaesthesiol Scand* 1997; 41:1033-1038.
70. Schoeffler P, Taxi J, Auroy P, Woda A, Bazin JE. Subarachnoid midazolam: Histologic study in rats and report of its effect on chronic pain in humans. *Reg Anesth Pain Med* 1991; 16:329-332.
71. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Granulomas (Inflammatory Masses). *Neuromodulation* 2012; 15:483-496.
72. Haering M, Saleh C, Jaszczuk P, Koehler M, Hund-Georgiadis M. Intrathecal pump catheter-tip granuloma recurrence with associated myelomalacia–How safe is intrathecal analgesic infusion therapy? A case report. *Surg Neurol Int* 2019;10.
73. Deer T, Hagedorn JM. How has ziconotide impacted non-cancer pain management?. *Expert Opin Pharmacother*. 2020; 21:507-511.
74. Kratzsch T, Stienen MN, Reck T, Hildebrandt G, Hoederath P. Catheter-tip granulomas associated with intrathecal drug delivery–a two-center experience identifying 13 cases. *Pain Phys* 2015; 18:E831-E840.
75. Duarte RV, Raphael JH, Southall JL, Baker C, Ashford RL. Intrathecal granuloma formation as result of opioid delivery: Systematic literature review of case reports and analysis against a control group. *Clin Neurol Neurosurg* 2012; 114:577-584.
76. Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion: A review of preclinical evidence and human data. *Pain Med* 2002; 3:300-312.
77. Toombs JD, Follett KA, Rosenquist RW, Benton LM. Intrathecal catheter tip inflammatory mass: A failure of clonidine to protect. *Anesthesiol* 2005 Mar; 102:687-690.
78. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression. *Drugs* 2011; 71:1807-1819.
79. Coffey RJ, Owens ML, Broste SK, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiol* 2009; 111:881-891.
80. Chen A, Ashburn MA. Cardiac effects of opioid therapy. *Pain Med* 2015; 16(suppl_1):S27-S31.
81. Mohammed I, Hussain A. Intrathecal baclofen withdrawal syndrome-a life-threatening complication of baclofen pump: A case report. *BMC Clin Pharmacol* 2004; 4:1-5.
82. Lee HM, Ruggoo V, Graudins A. Intrathecal clonidine pump failure causing acute withdrawal syndrome with 'stress-induced'cardiomyopathy. *J Med Toxic* 2016; 12:134-138.
83. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for intrathecal drug delivery: Guidance for improving safety and mitigating risks. *Neuromodulation* 2017; 20:155-176.
84. McDowell GC, Saulino MF, Wallace M, et al. Effectiveness and safety of intrathecal ziconotide: final results of the patient registry of intrathecal ziconotide management (PRIZM). *Pain Med* 2020; 21:2925-2938.
85. Deer T, Krames ES, Hassenbusch SJ, et al. Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: Report of an interdisciplinary expert panel. *Neuromodulation* 2007; 10:300-328.
86. Pope JE, Deer TR. Ziconotide: A clinical update and pharmacologic review. *Expert Opin Pharmacother* 2013; 14:957-966.