Narrative Review

Intrathecal Drug Delivery for Chronic Pain Syndromes: A Review of Considerations in Practice Management

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

Conflict of interest: TD is a consultant for Abbott, Axonics, Bioness, Nalu, Saluda, Vertos, Vertiflex, Spinethera, Flowonix, and Cornorloc. AA-E is a consultant for Medtronic, StimWave, and Avanos. All other 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: 01-06-2020
Revised manuscript received: 03-01-2020
Accepted for publication: 04-16-2020

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Background: Chronic pain syndromes are poorly understood and challenging to treat. However, intrathecal drug delivery systems (IDDS) have been shown to have good efficacy in treating various pain subtypes and patient populations. The success of IDDS interventions is largely dependent on consideration of and adherence to varying practice patterns.

Objectives: We aimed to review and report on the evidence basis for various considerations in IDDS practice management including: (1) patient selection and periprocedural criteria, (2) efficacy of IDDS for various conditions, (3) intrathecal medications, (4) drug delivery systems, (5) trial and implantation, (6) complications and adverse events, and (7) chronic follow-up.

Study Design: We conducted an evidence-based narrative review.

Methods: PubMed, Medline, Cochrane Library, prior systematic reviews, and reference lists were screened by 2 separate authors for all randomized trials, meta-analyses, and observational studies relevant to each of the aforementioned management principles and were considered for study inclusion.

Results: All high-level evidence studies that explored the various facets for IDDS practice management were included for review.

Limitations: Despite existing evidence basis for practice considerations, current practice patterns are highly practitioner dependent. More and continued high-level evidence is necessary to support, affirm, and dictate principles in practice considerations.

Conclusions: Incorporation of the principles found in this evidence-based narrative, which is comprised of the highest level of evidence supportive of various facets of IDDS practice management, is essential to optimize outcomes, treatment efficacy, and safety profiles.

Key words: Chronic pain, intrathecal drug delivery, practice management

Pain Physician 2020: 23:E591-E617

Chronic pain is a pathological phenomenon that remains poorly understood and challenging to treat (1-3). However, prevailing and largely accepted theories suggest that inappropriately sustained and/or aberrant activation of the ascending pain pathways leads to central pain sensitization (3,4). Unfortunately, this neuroplasticity leads to a high treatment failure rate with pharmacologic options, including opioids. Neuromodulation, by way of spinal cord stimulation or intrathecal drug delivery, however, has been found to have good efficacy (5-7). In certain pain conditions, such as refractory cancer pain,

intrathecal analgesia has been found by several high-quality and well-designed studies to be considerably superior to standard medical management (8,9).

The use of intrathecal drug delivery systems (IDDS) has been readily utilized for various refractory chronic pain syndromes across the past decade (6,9). The success of IDDS interventions is dependent on a multitude of factors ranging from appropriate patient selection and periprocedural protocols to judicious management of complications and adverse events. Given the extensive breadth and depth of these multiple facets of IDDS management in the context of a paucity of comprehensive, overarching, and readily generalizable literature for key IDDS management principles, this publication is aimed at appraising the available literature and presenting the currently available evidence for (1) patient selection and periprocedural criteria, (2) efficacy of IDDS for various conditions, (3) intrathecal medications, (4) drug delivery systems, (5) trial and implantation, (6) complications and adverse events, and (7) chronic follow-up.

Methods

Study Design

This study was an evidence-based narrative aimed at appraising the available literature for various facets for IDDS management. Although a meta-analysis was initially considered, the authors found that there existed a large degree of heterogeneity in pain syndromes, intrathecal interventions, and outcomes gathered to meaningfully conduct a high-quality meta-analysis.

Data Sources

PubMed, Medline, Cochrane Library, prior systematic reviews, and reference lists surveyed from 1966 through July 2019.

Study Selection

All randomized trials, meta-analyses, and observational studies relevant to each of the aforementioned management principles were identified and allocated to their relevant section(s). Studies for sections such as patient selection and periprocedural criteria, in which IDDS-specific literature was sparse, were gathered largely from surveyed reference lists. Inclusion criteria included those human studies in the English language with a sample size of at least 10 persons that had pertinent relevance to the aforementioned IDDS management practices of interest. All studies were independently appraised and collected by 2 separate authors. No outside funding was provided for this assessment.

Results

Utilizing the aforementioned search and study selection strategy, we identified a total of 117 studies to be included in our evidence-based narrative (Fig. 1).

Discussion

Patient Selection Criteria and Periprocedural Management

To provide the best outcomes for patients considering IDDS, physicians should complete a thorough investigation into patient appropriateness for the procedure. This selection criteria should be utilized to not only identify those patients with appropriate pain syndromes amenable to IDDS therapy, but also those persons with acceptable preprocedural medical risk profiles and outcome expectations. Consequently, careful patient selection criteria can serve to confer better outcomes, fewer complications, and even lessen health care burden overall. Criteria for consideration include risk of bleeding, opioid abuse, psychological comorbidities, and infection.

Bleeding Risk

Most procedures contain some degree of bleeding risk. Procedures such as IDDS placement are considered high risk by the Neurostimulation Appropriateness Consensus Committee (NACC), the American Society of Interventional Pain Physicians (ASIPP), and the American Society of Regional Anesthesia and Pain Medicine (ASRA) due to their high bleeding risk and close proximity to high-risk areas, namely the spine and its associated vasculature, neurologic structures, soft tissue, and lymphatic networks (10-13). Fibrous adhesions or scar tissue associated with these procedures can compress epidural vessels or infringe into epidural space. Epidural hematomas from vascular damage with these procedures, although rare, can also lead to cord compression and result in devastating neurologic outcomes, including paraplegia or paraparesis (10-14). As IDDS placement falls into the category of procedures performed in the cervical, thoracic, or high lumbar spine (above L5-S1, where there is less space for hematomas to occur asymptomatically), it is regarded as a high-risk procedure (13). Furthermore, patient-specific considerations, such as comorbid medical conditions, coagulopathies, and anticoagulant use, can add additional

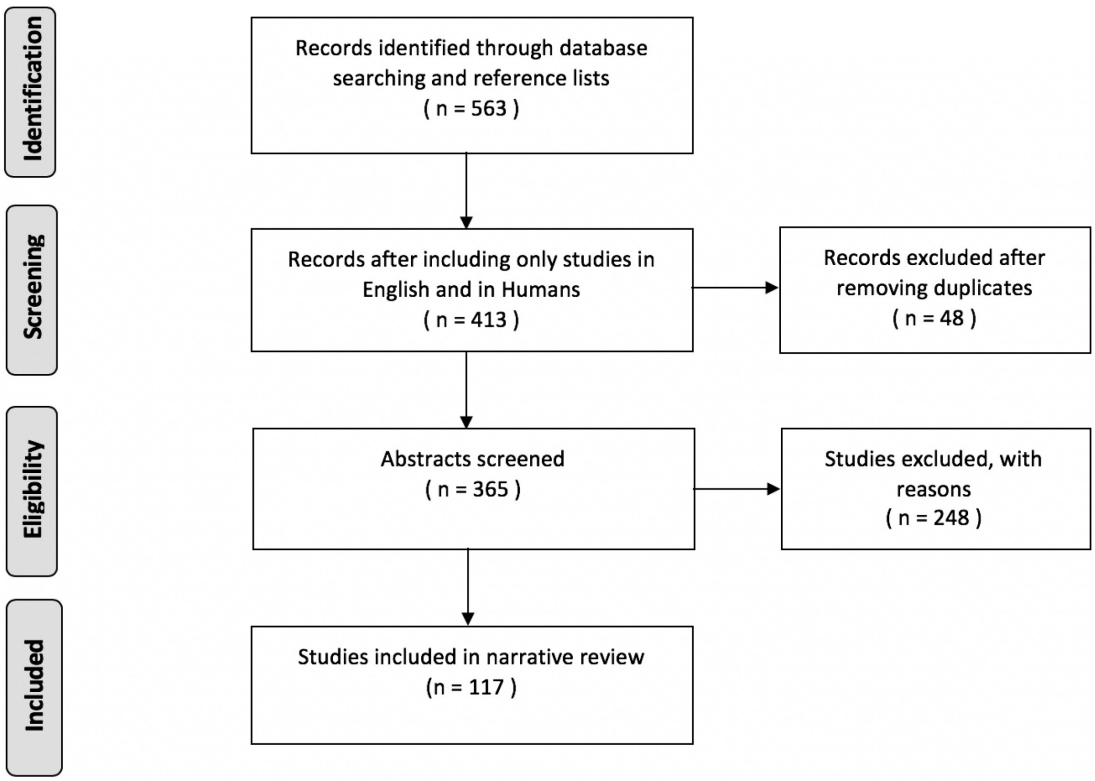

Fig. 1. *PRISMA flowchart delineating study selection.*

risk to this procedure and must be factored into risk assessment on an individual basis.

The decision on this issue of the risk to benefit ratio of discontinuing a medication used for prophylaxis in the setting of cardiac or thrombotic risk should be determined by the prescribing physician of the medication. Given that IDDS placement is elective, a careful assessment of procedural bleeding risk is compulsory.

Anti-Platelet Agents

Anti-platelet agents are varied and include nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin (ASA), phosphodiesterase (PDE) inhibitors, P2Y12 inhibitors, and glycoprotein IIb/IIIa inhibitors.

NSAIDs

NSAIDs, which are conventionally differentiated from ASA, inhibit cyclooxygenase (COX)-mediated prostaglandin production, thereby decreasing inflammation. NSAIDS may be nonselective in COX inhibition or demonstrate selectivity to COX-1 or COX-2, which are associated with increased gastrointestinal (GI) or cerebrovascular risks, respectively. Notably, COX-1 selective NSAIDs confer greater platelet dysregulation and decrease in primary hemostasis. Although COX-2 affects prostacyclin synthesis, which has antiplatelet effects, COX-2 selective NSAIDs do not need to be stopped prior to high-risk procedures, as they are found not to alter platelet function despite elongated periods of supratherapeutic doses (10-13,15).

Per ASRA, it is within guidelines to hold NSAIDs with COX-1 inhibiting action for 5 half-lives, until 3% of the drug is left in the system, and enough time is given to render its antiplatelet effect inactive. NSAIDs can be restarted 24 hours after the procedure.

ASA

ASA medications—mechanistically NSAIDs—are often utilized for cardiac and cerebrovascular protection. The risk stratification of holding ASA should involve the patient, the pain physician, and the physician

who prescribes the ASA to weigh the risk of procedural bleeding versus cardio- and cerebrovascular risks (16).

If the patient takes it for primary prophylaxis, that is to prevent development of a disease in a patient without prior history, ASRA guidelines recommend discontinuing for high-risk procedures, such as IDDS placement for 6 days prior, whereas ASIPP recommends discontinuing for 4 days prior (12,13).

For high-risk procedures, ASRA strongly recommends considering the discontinuation of ASA. ASA can be resumed 24 hours after the procedure in both situations. To clarify, ASRA, ASIPP and NACC guidelines primarily address 81-mg dosages of ASA. Research regarding hemorrhagic risks of 325-mg dosages of ASA is limited, especially in the case of IDDS placement, although one study concerning epidural steroid injections (regarded as an intermediate-risk procedure by ASRA, high-risk by ASIPP) in patients on 325-mg dosages of ASA did not show increased hemorrhagic complications (12,17,18). Furthermore, a 2007 study by Campbell et al (17) demonstrates that daily long-term use of doses higher than 81 mg has not shown to improve efficacy in prevention of adverse cardiovascular events.

PDE Inhibitors

For PDE inhibitors such as cilostazol and dipyridamole, recommendations vary based on whether they are used in combination with ASA. For cilostazol and dipyridamole alone, a holding period of 48 hours prior to a procedure is recommended per ASRA and NACC (10,12,19). Per ASIPP, if used without ASA, they are safe to continue in interventional procedures (13,20). If used in combination with ASA, ASRA and NACC states that recommendations for discontinuing ASA for high-risk procedures should be followed. The combination of ASA and dipyridamole has been suggested to increase bleeding risk (21).

P2Y12 Inhibitors

For P2Y12 inhibitors such as clopidogrel, prasugrel, ticagrelor, or cangrelor, considerations must be made pertaining to patient's age, history of abnormal bleeding, liver or renal disease, and concomitant use of other antiplatelet medications. These must be weighed against the patient's risk for thrombosis. Discussions should also be had with the patient's prescribing physician. Although for low-risk procedures it may be possible to continue use of P2Y12 inhibitors, more stringent guidelines exist for high-risk procedures, such as IDDS placement.

Per ASRA/NACC guidelines, clopidogrel should be held for 7 days and can be restarted 12 to 24 hours after the procedure (12 hours for daily dose, 24 hours if patient requires loading dose) (10,12). Prasugrel should be held for 7 to 10 days, and ticagrelor for 5 days prior, both can be restarted 24 hours after the procedure (10,12). Cangrelor should be stopped for a minimum of 3 hours prior to the procedure (10,12). For those at high risk of thromboembolic events, a bridge with low-molecular-weight heparin (LMWH) can be instituted that is set to stop 24 hours before the procedure. With these recommendations in mind, it must be considered that there is limited evidence demonstrating the efficacy of discontinuing P2Y12 inhibitors in prevention of bleeding complications (13).

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors are commonly used in percutaneous coronary interventions due to their potent antiplatelet effects and include the medications abciximab, eptifibatide, and tirofiban. No studies exist studying their effects and interactions with interventional pain procedures (12,13).

Based on ASRA guidelines, 5 days discontinuation for abciximab is considered adequate, whereas 24 hours discontinuation for eptifibatide and tirofiban is most likely adequate. Restarting the medications 8 to 12 hours after the procedure is recommended (12).

Anticoagulants

This class of medications includes warfarin, heparin, fibrinolytic agents, and novel oral anticoagulants (NOACs).

Warfarin

Good evidence exists supporting the discontinuation of warfarin prior to interventional techniques, as warfarin use in interventional procedures is frequently associated with case reports of epidural hematomas—in some cases even when warfarin is stopped appropriately (13). For high- and intermediate-risk pain procedures, such as IDDS placement and IDDS-related procedures, ASRA recommends stopping warfarin for 5 days prior in addition to international normalized ratio (INR) ($\leq$ 1.2). For patients who continue to have elevated INRs after holding warfarin, ASRA guidelines recommend vitamin K if there is no bleeding. If there is life-threatening bleeding, recombinant factor VIIa, 3-factor prothrombin complex concentrate (PCC), or 4-factor PCC can be given. Warfarin can be started

the day after the procedure. For those at high risk of thrombosis, bridging with LMWH is advised after consulting with the treating physician (12). The data on the benefit of an LMWH bridge is controversial in the literature (22,23). Acenocoumarol, which works via the same mechanism as does warfarin and is more commonly used in Europe, should be stopped for 3 days prior to the procedure and the INR normalized (10,12).

Heparin

Patients on intravenous (IV) heparin are not ideal for high-risk spinal and pain procedures, as it is generally recommended to use alternative pain treatments until the patient can come off of IV heparin. If the procedure needs to be completed, IV heparin should be stopped at least 4 to 6 hours prior to any procedure. If the procedure is intermediate or high risk, 24 hours should be allowed to pass before IV heparin is restarted (10,12).

Subcutaneous heparin has also been frequently implicated in cases of epidural hematoma (22-24). Patients on subcutaneous heparin, similar to those on IV heparin, are not ideal for pain procedures, and situations in which patients need to have their subcutaneous (SQ) heparin held for interventional pain procedures should be avoided. For high-risk procedures, including IDDS placement, ASRA recommends waiting an interval of 24 hours between the last dose of SQ heparin and the procedure. SQ heparin can be restarted 6 to 8 hours after IDDS.

Fibrinolytics

Pain procedures should especially be avoided in patients who need fibrinolytic agents, such as tPA (tissue plasminogen activator). Multiple case reports of spontaneous spinal hematoma in patients on fibrinolytic medications have been published, as well as spinal hematomas in patients undergoing spinal-cord procedures, suggesting that the medications require the utmost of caution even in the absence of high-risk procedures, such as IDDS placement/modification (25-27). If pain procedure must be performed, 72 hours should elapse between discontinuation of fibrinolytic agent and a high-risk pain procedure. If an emergency situation arises causing a patient to require a fibrinolytic agent after a neuraxial procedure, the pain provider should be notified. IDDS should be left in place until 48 hours after the agent is used or a minimum of 2 half-lives of the drug has passed, after which it should be removed (12).

NOACs

All NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, are direct Xa inhibitors. Per ASRA, a 5 half-life discontinuation period is recommended for high-risk pain procedures (12). For those at high risk of venous thromboembolism (VTE), LMWH bridge can be considered. All drugs can be resumed 24 hours after a procedure. If VTE risk is high, half of the usual dose can be resumed 12 hours after. Certain caveats exist for each medication. For dabigatran users with end-stage renal disease, NACC recommends extending the 4-day discontinuation period to 5 to 6 days as the half-life increases in these patients (10,13). For those at high risk of VTE, dabigatran can potentially be restarted within 12 hours after discussion by the treating physician (10-12).

Fondaparinux is a synthetic anticoagulant that blocks factor Xa, generally used in the aftermath of major orthopedic surgery or initial treatment of pulmonary embolism. Data are scarce on the risk of spinal hematomas in users of fondaparinux, with a study of 1,603 patients with neuraxial catheters or deep peripheral nerve catheters showing no complications (28). ASRA recommends a 4-day discontinuation of fondaparinux (5 half-lives) prior to a high-risk procedure, which can be restarted 24 hours after the procedure (12).

Miscellaneous Medications and Supplements

Selective serotonin reuptake inhibitors (SSRIs), when used in conjunction with antiplatelet medications or anticoagulant medications, have been shown to increase the risk of both GI and non-GI bleeding (29,30). Although they are not routinely discontinued before pain procedures as uncontrolled depression worsens outcomes, ASRA recommends they should be gradually tapered and stopped 1 to 2 weeks before high-risk procedures, including IDDS, if the depression has been stable (31). Fluoxetine has to be tapered for longer, 5 weeks, due to its longer half-life (32). If depression is unstable, the SSRI can be switched to bupropion, Remeron, or a tricyclic antidepressant. The decision to stop these medications should be made by the physician treating the underlying depression. SSRIs can be restarted as soon as possible after the bleeding risk stops, which in many cases is the next day.

Always inquire about use of herbal supplements as they can interact with patient's medications or independently act as bleeding risk factors. Culprits include garlic, dong quai, danshen, gingko biloba, and panax ginseng. A 1-week discontinuation period is adequate

for most herbal products that can increase bleeding risk. For garlic, antiplatelet effect is dose-dependent, and daily dose of garlic intake should be documented (33). If patients with several comorbidities take more than 1,000 mg/day, or if they are also taking ASA, NSAIDs, or SSRIs, platelet function tests should be ordered. In patients taking warfarin and dong quai or warfarin and danshen, ASRA recommends checking INR. Additionally, in patients taking gingko biloba and an antiplatelet agent, platelet function should be tested.

Per ASRA, dietary supplements such as vitamin E and fish oil should be treated like antiplatelet agents and discontinued as such prior to high-risk procedures (34,35). Medications such as pentosan polysulfate sodium should be discontinued 5 days prior to high-risk procedures and started 24 hours after.

Opioid Abuse Screening

Patients who have prior and/or current opioid abuse or untreated addiction disorders may not be appropriate candidates for IDDS. It is thought that those persons with demonstrated patterns of opioid abuse exhibit maladaptive coping patterns, which are not likely to be corrected with IDDS placement. Therefore screening for and differentiating those persons with appropriate and inappropriate opioid use can help to identify those persons who may also be appropriate and inappropriate, respectively, for IDDS placement. The increased emergence and use of state programs for the monitoring of distribution of controlled substances has helped to screen those patients who may be appropriate recipients of opioids for chronic pain. One study by Baehren et al (34) indicated that Ohio-based physicians changed the prescription plan 41% of the time after reviewing the online database.

A study by Webster and Webster (35) demonstrated that the Opioid Risk Tool was an effective screening tool to risk-stratify patients based on several risk factors to assess who was more likely to exhibit aberrant behaviors related to opioid use (36). In patients with chronic non-cancer pain, family history of substance abuse, history of legal issues, and substance abuse increases risk for aberrant behaviors with future opioid use, as shown by Michna et al (36). In a large retrospective chart review of 3,040 patients conducted by Page et al (37), pain duration, quality of life, and cigarette smoking were identified as risk factors for opioid abuse, which in turn predicted outcomes at 6-month follow-up. Similarly, a prospective study of 196 patients by Ives et al (38) identified younger age, male gender, prior substance abuse, and prior drug or DUI conviction as risk factors, although interestingly, depression score and pain score were not. One population where special consideration should be undertaken is patients who have sleep apnea along with chronic pain. Webster et al showed that there is a dose-response relation between sleep apnea and chronic opioid use (35). Opioid abuse, either historically or currently, predicts possible poor outcomes in persons considered for IDDS placement. A thorough investigation of patient risk factors is thus necessary for IDDS to determine appropriateness. In the setting of recovery from the historical addiction, the use of IDDS is often appropriate, but a preassessment by a psychological expert is recommended prior to implant (39,40).

Preprocedural Opioid Weaning

Given the current opioid crisis and the lack of strong evidence supporting long-term systemic opioid use for pain control, IDDS serves as a beneficial alternative to long-term systemic opioid use by allowing the patient to intake significantly lower doses of pain medication (41-43). For patients who are receiving IDDS for the purposes of pain control, it is recommended to first taper off of all preexisting opioid medications if clinically possible (44,45). This can be tailored to specific patient needs and tolerance. Grider et al (42) report a drug holiday of up to 6 weeks is recommended. When possible, this method allows providers to titrate to the lowest effective dose. The opioid holiday is also shown to result in lower effective IDDS doses in patients than in those who do not undergo an opioid holiday (44). The combination of tapering off medications and taking a drug holiday also help minimize adverse effects associated with opioids and may improve IDDS outcomes. This may not be possible in those with significant nerve compression, bone collapse, or tissue destruction from metastatic disease, and a case-by-case decision algorithm should be used in this patient group.

Psychiatric Screening

It is recommended practice to have a tailored psychological assessment as part of the patient selection process for IDDS during the pretrial or preimplant phase. This screening is of particular importance given that the prevalence of psychiatric disorders is higher in persons with chronic pain relative to the general population. Screening generally consists of a 1-hour clinical interview that develops a functional patient

description, which offers context for pain behavior. The evaluation may involve a psychological specialist who acts as a consultant, but the evaluation does not always require a specialist if they are not available. The evaluation aims to highlight characteristics that may positively or negatively impact the trial or long-term therapy efficacy. Psychiatric conditions have been extensively shown to influence the success rates of IDDS. Absolute contraindications for IDDS placement include suicidal depression, schizophrenia with active psychotic behavior, active suicidal or homicidal tendencies, or active substance abuse (46). Moreover, there exists a black box warning against use of intrathecal (IT) ziconotide in persons with preexisting psychotic disorders given its adverse effect profile (47,48).

Even in cancer patients receiving IDDS, a less-studied population, preprocedural psychological evaluation can have value. One study examining IDDS in cancer patients reports that although baseline anxiety or depression did not have an effect on pain at follow-up assessments, baseline anxiety scores did tend to increase the trajectory of pain scores over time (49). Thus evaluating this population prior to IDDS could identify which patients may benefit from a greater level of comprehensive care or cognitive behavioral treatment prior to implantation.

Despite the positive relationship between psychological factors and poor treatment outcomes, it is difficult to pinpoint specific psychological pathology or isolate any one factor that worsens outcomes in the context of IDDS. Even contraindications to IDDS listed earlier are based more on experience than on scientific validation. Data from patients receiving spinal cord stimulation for pain control does show that certain factors, such as tobacco use or sleep interference, have been identified as independent factors associated with poor outcomes (50,51). This may cause the prognostic value of psychological assessment in IDDS to be uncertain. Regardless, it has value in identifying psychological factors that can be addressed, as well as identifying patients who may need more education or addressing of expectations.

As aforementioned, opioid abuse patterns may render patients poor candidates for IDDS therapy. Notably, many persons with psychiatric illnesses (namely mood disorders) also have high rates of opioid abuse. Not unexpectedly, opioid use itself may be a risk factor for developing depression. Scherrer et al (50) reviewed 49,770 patient charts retrospectively and found that the risk of developing depression increased as opioid duration increased. Additionally, Mohanty and Senjam (51) studied 80 patients with opioid dependence syndrome and discovered that 77.5% of them had psychiatric comorbidities, with depression and suicidality as the predominant conditions. Thus careful screening for both risk factors in imperative for appropriate patient screening. Interestingly, treating these disorders may also increase IDDS therapy itself. Molloy et al (52) found that cognitive behavioral therapy as an adjunct to IDDS was superior to either intervention alone.

In a study done by Wasan et al (53), patients were classified as high or low risk for psychiatric morbidity based on self-reported symptoms and history on various forms and questionnaires. Of note, the patients in the high-risk group showed increased prescription opioid misuse tendencies, evidenced by the screening tools Screener and Opioid Assessment for Pain Patients (SOAPP) and Current Medication Misuse Measure (COMM) (54). Jamison et al (54) used a Drug Misuse Index (DMI) as a risk stratification tool in their prospective study of 42 patients. The DMI consisted of a self-reported Prescription Drug Misuse Questionnaire, urine toxicology reports, and physician-reported Addiction Behavior Checklist; this tool aided their discovery that behavioral intervention could improve opioid compliance in patients with high risk for prescription opioid misuse.

Prior to an IDDS trial, a psychiatric assessment of the patient should be conducted to screen for psychiatric morbidity. Unevaluated or uncontrolled psychiatric issues may result in unrealistic patient expectations, exacerbation of chronic pain syndromes, and low efficacy and adverse outcomes following IDDS placement.

Infectious Risk

Reported infection rates for intrathecal pump systems vary greatly from center to center but minimizing infection rates is especially important due to high morbidity associated with implant-related infections, including neuraxial abscesses and meningitis (55,56). Various multicenter studies report infection rates ranging from 3% to 15% (14,57). In pediatric populations, baclofen pumps for dystonia and spasticity have reported infection and complication rates that range from 3% to 41.7% (58,59). As the use of IDDS has increased in the past decade as a treatment for pain, spasticity, and dystonia, it is especially important to address factors that may result in minimizing infection rates. As a pocket in the subcutaneous tissue starts to heal, fibrous tissue encases the device at the pump site, which limits

the blood supply. This may limit healing and increase the risk of infection in immunocompromised patients. Inert elements are also prone to biofilms that grow on the surface, creating matrices that make it difficult to penetrate and treat with antibiotics, leading to treatment failure and ultimately removal of IDDS systems (60). Furthermore, because these systems are often manipulated and refilled after initial implantation, this presents a higher risk of infection than performing only one procedure. The most frequently found organism in IDDS infections are staphylococcal infections, with Staphylococcus aureus and Staphylococcus epidermidis biofilms being widely implicated in chronic implant-based infections (60).

There is a lack of well-established diagnostic criteria for what constitutes an infection. A 2017 retrospective analysis of 288 IDDS surgeries show there are no clear diagnostic guidelines or specific triggers that lead to infection workup (58). Furthermore, different providers view what constitutes infectious signs and symptoms differently (60). This factor may also contribute to the wide range of infection rates reported in the literature.

Multiple recent studies exist testing the effect of certain controllable factors on infection rates. Notable factors contributing to higher infection rates include lack of provider experience and longer surgical durations (60). A 2019 retrospective single-institution, single-surgeon study enacted a care bundle approach for neurosurgical implants. This care bundle included preoperative counseling, questionnaires, hygiene instructions, infection screens, nasal methicillin-resistant S. aureus and methicillin-susceptible S. aureus decolonization, body decolonization, preoperative antibiotics, and strict sterile operating room techniques (59). The care bundle as a whole was shown to significantly decrease infection rates for IDDS procedures observed in both 90-day and 1-year follow-ups (61). A similar study examining baclofen IDDS systems in pediatric populations enacted care bundles, and standardized protocols also showed significant reduction in infection rates as a result (62). However, owing to the nature of the care bundles, independent factors contributing to lower infection rates were not identified.

Care bundles contain antibiotic use, which is an important starting point in looking for individual factors that affect infectious outcomes, both because of the importance of antibiotic stewardship and the conjecture-based efficaciousness of antibiotics compared with other preventative tactics. The necessity of perioperative antibiotics seems intuitive but exact details are not well delineated. Are preoperative antibiotics more effective than intraoperative antibiotics? How long of a duration is needed? Do local antibiotics improve outcomes while decreasing risks of resistance? A study examining the efficacy of intraoperative vancomycin powder in IDDS procedures showed that this factor did not reduce infection rates in the study population and actually increased infection rates compared with institutional controls, although the power (n = 26) was extremely limited (55). Local vancomycin used intraoperatively was later shown to effectively reduce surgical site infections in rodents (n = 64) on short-term follow-up (26). This factor may warrant further study on larger patient populations. Although intra- and postoperative antibiotics may not be justifiable in these patients, a 2015 study of IDDS in pediatric populations showed a subgroup of patients who missed preoperative antibiotics had a significantly higher 6-month surgical infection and complication rate (61,63). At the very least, care bundles should include preoperative antibiotics, as these are shown to be the most necessary in the literature, as compared with intra- or postoperative antibiotics.

Special Considerations

Economics may play a role in patient selection as well. In a survey conducted by Deer et al (62), practitioners were not satisfied with insurance reimbursement, workers compensation, and inadequate payment for practice costs (74.7%, 65.1%, 90.5%, respectively).

In a small case series of 20 patients by Dunbar and Katz (63), patients who did not abuse opioids were more likely to have a stable support system, report isolated alcohol abuse, and be active members in Alcoholics Anonymous; patients who did abuse opioids were more likely to have polysubstance abuse or history of oxycodone abuse.

Assessment of chronic pain in cancer patients and IDDS initiation may require more special attention. Engle et al (64) showed that postoperative infection was rare in patients with cancer, and there was not a significant difference in infection rates between cancer and non-cancer patients. Scanlon et al (65) studied IDDS implantations in cancer patients, and 6.2% had developed surgical site infections, which is on the high end of the national surgical site infection rate. However, that effect may have been influenced by steroid use, radiation therapy, and immunomodulator use.

Deer et al (62) surveyed 87 physicians about intrathecal therapy, and 63.9% of them reported granu-

loma formation in a patient, of which 66% reported neurologic injuries secondary to the granuloma.

Efficacy and Indications

There exists an abundance of literature supportive of IDDS as an efficacious intervention for many nociceptive, neuropathic, and mixed-type chronic pain syndromes. Additionally, the indications for IDDS therapies are varied but are largely and conventionally divided into cancer and non-cancer pain indications. Notable non-cancer pain indication span axial back pain and complex regional pain syndrome (CRPS) among others (9,44,62). Regardless of the underlying etiologies, IDDS is thought to be most efficacious for discrete pain presentations relative to those of vague, generalized chronic pain. Moreover, the effectiveness of IDDS is also largely dependent on the choice of IT analgesic medications utilized.

The aforementioned available literature spans from sentinel prospective cohort studies to well-designed randomized controlled trials (RCTs), which have collectively helped to establish our current understanding and appreciation of IDDS effectiveness. Careful consideration of both the pain syndrome presentation and IT medications to be utilized is instrumental in dictating IDDS efficacy.

Chronic Cancer Pain

A majority of patients with cancer experience chronic pain that can often be distressing and functionally debilitating. Moreover, with ever-increasing cancer survivorship in recent years, so too exists an increase in the overall prevalence of cancer pain (8). These pain presentations, largely varied on the specific cancer disease characteristics, are often mixed nociceptive-neuropathic and can be sequelae of tumor burden or the cancer treatments themselves, such as surgical resection, chemotherapy, and/or radiation therapy. Consequently, managing these varied and complex pain syndromes can be challenging. Many affected patients often fail to achieve effective analgesia with chronic medical management alone and/or are susceptible to opioid-related adverse effects. Thus interventions such as IDDS therapy carry much promise in both conferring effective pain relief and reducing systemic opioid use.

Much of the evidence for IDDS efficacy in cancer pain is derived from the work of Smith et al (40) in 2002, Staats et al (66) in 2004, and a few others (5,39,67-72) (Table 1). Smith et al (40) investigated the analgesic benefit of IT opioids in treating refractory chronic pain in persons with advanced cancers. Patients were divided into comprehensive medical management (CMM) or CMM with concomitant morphine or hydromorphone treatment arms. However, across the course of the study, some patients received treatments other than what was initially ascribed, and so an as-treated group analysis was also undertaken. Nonetheless, both randomized group and as-treated group analyses showed that IT opioid therapy was not only superior to CMM in pain reduction across a 6-month follow-up period, but also that it was associated with fewer opioid-related side effects. Following these landmark trials, Rauck et al (39) corroborated that IT morphine confers greater than 50% efficacy in refractory cancer pain and considerable systemic opioid reduction. Additionally, they showed that these benefits were long-term noting their follow-up period of up to 16 months.

Staats et al (66) explored the analgesic efficacy of IT ziconotide in a cohort of persons with refractory cancer or AIDS chronic pain. This well-designed, double-blinded, and placebo-controlled RCT across 32 centers found that persons with IT ziconotide had 53% improvement in mean Visual Analog Scale of pain intensity scores relative to a 18% improvement in the placebo study arm at the end of an 11-day follow-up period. Subsequently, Wallace et al (75) in 2008 and Webster et al (76) in 2009 explored the safety and tolerability of IT ziconotide across a short-term (2 months median) and long-term (36 months) follow-up period, respectively. Wallace et al (75) found that most adverse effects that occurred in 99% of persons in a 644 person cohort were mild or moderate and did not hamper tolerability. Similarly, Webster et al (76) found that IT ziconotide continued to be effective and safe in a long-term follow-up scale.

Chronic Non-Cancer Pain Syndromes

As previously stated, those persons with clearly defined pain pathophysiology tend to be better responders to IDDS intervention relative to those with vague and diffuse pain presentation (44,62,75). Consequently, the highest level of evidence supportive of IDDS for non-cancer pain exists for CRPS and axial back pain, either back and leg pain, or failed back surgery. However, there also exists a score of evidence for chronic unspecified non-cancer pain.

CRPS

There does not appear to be any clinical standard for IT medications for treating CRPS. A limited subset of

Table 1. *Highest available evidence for use of IDDS in treating chronic cancer pain.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Smith 2002 (40)	IT morphine vs. CMM	Refractory cancer pain, n = 142	Multicenter RCT, I	Pain relief, opiate adverse effect reduction	6 months	IT morphine produced significant analgesic benefit, reduction in systemic opiate adverse events, and interestingly, improvement in survival.
Staats 2004 (66)	IT ziconotide	Refractory cancer or AIDS pain, n = 105	Multicenter RCT (DB+PC), I	Pain relief	10–11 days	IT ziconotide produced significant analgesic benefit.
Rauck 2003 (39)	IT morphine	Refractory cancer pain, n = 119	Multicenter, Prospective, II	Pain relief, opiate reduction, opiate adverse effect reduction	Up to 16 months	IT morphine produced significant analgesia (>50% reduction in pain) and reduction in systemic opiate intake.
Wallace 2008 (73)	IT ziconotide across time	Cancer or AIDS pain, n = 644	Multicenter, Prospective, II	Safety and tolerability	2 months median	Most adverse effects (prevalence of 99% in cohort) were mild or moderate.
Webster 2009 (74)	IT ziconotide across time	Chronic pain from cancer AND non-cancer, n = 78	Multicenter, Prospective, II	Long-term safety, pain relief	36 months	Long-term IT ziconotide was safe, well tolerated, and produced sustained analgesia.
Alicino 2012 (67)	IT ziconotide + IT morphine	Refractory cancer pain, n = 20	Prospective, II	Safety and efficacy	1 month	Combination of IT ziconotide and IT morphine was safe, effective, and provided rapid analgesia.
Onofrio 1990 (68)	IT morphine	Pain from end-stage cancers (metastatic and terminal), n = 53	Prospective, II	Efficacy and safety	4 months	Long-term IT morphine analgesia was safe and effective.
Penn 1987 (5)	IT morphine	Chronic pain (N = 43), in which cancer pain was majority (n = 35)	Prospective, II	Pain relief, opiate reduction, function	Mean 5–6 months	IT morphine is safe and effective.
Mercadente 2007 (69)	IT morphine + levobupivacaine	Refractory cancer pain, n = 55	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + levobupivacaine produced significant analgesia and opiate reduction, with safety.
Sjoberg 1991 (70) and Sjoberg 1994 (71)	IT morphine + bupivacaine 1994 study utilized a 1:10 morphine to bupivacaine ratio	Refractory cancer pain, n = 52	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + bupivacaine was safe and effective, a 1:10 ratio was deemed efficacious, but with bupivacaine adverse effects noted in almost half of patients.
Dupoiron 2012 (72)	IT ziconotide + morphine, ropivacaine, clonidine	Refractory cancer pain, n = 77	Prospective, II	Pain relief	3 months	IT ziconotide in combination with other IT agents was safe and effective.

DB, double blinded; PC, placebo-controlled

prospective studies exists with each exploring different medications in different populations, the largest of which involves a sample size of 42 persons (Table 2). For refractory CRPS, Rauck et al (76) found that both IT clonidine and adenosine were effective analgesics across a 2-hour follow-up, whereas Herring et al (78) found benefit with IT ziconotide across a 4 or more year follow-up. Of note, Herring et al (77) also found that IT ziconotide decreased oral opioid use across this chronic stage. Overall, however, higher level evidence exploring IDDS for CRPS specifically is largely lacking (78-80).

Axial Back Pain

There exist many studies supportive of IDDS for

Table 2. *Highest available evidence for use of IDDS in treating CRPS.*

Author and Year	Intervention	Patient Type and Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Rauck 2015 (57)	IT clonidine vs. IT adenosine	Pain and hyperalgesia in a lower extremity from CRPS, n = 22	Double-blind crossover, I	Efficacy, pain characteristics	2 hours	Both IT clonidine and IT adenosine produced reductions in hyperalgesia and analgesia.
Van der Plas 2013 (78)	IT baclofen	CRPS with dystonia, n = 42	Prospective, II	Pain efficacy, dystonia severity, opiate reduction	52 weeks	Analgesia occurs increasingly for up to 6 months and then plateaus despite increases in IT baclofen dose and continued improvements in dystonia.
Van der Plas 2011 (79)	Slow vs. fast IT baclofen regimens	CRPS with dystonia, n = 13	Double-blind crossover, I	Efficacy and safety	4 weeks	Both slow and fast IT baclofen regimens produced similar reductions in pain and dystonia, but fast titration group was associated with more adverse effects.
Munts 2009 (80)	IT glycine vs. saline solution	CRPS 1 with dystonia, n = 19	Double-blind crossover, I	Pain, dystonia	4 weeks	IT glycine did not produce any meaningful reduction in pain or dystonia.
Herring 2019 (77)	Various IT medications	CRPS, n = 26	Retrospective review, III	Pain intensity, oral opiate intake	4 or more years of follow-up	No one IT medication led to decreased pain intensity across time; only IT ziconotide was associated with decrease in oral opiates.

use in treating axial back pain, with one RCT and several prospective cohort studies. Of note, IDDS is thought to have a role in treating persons with back and/or leg pain who failed spinal cord stimulation treatment (7,44,62). A landmark study—an RCT by Serrao et al (81)—found that IT midazolam was not only as effective as epidural methylprednisolone injections in delivering pain relief, but also those in the IT group demonstrated reduction in opioid use and opioid-associated adverse effects. Many other well-designed prospective studies also report efficacy of IT morphine in conferring pain reduction in chronic low back pain. Notably, studies by Winkelmüller et al (82) and Rainov et al (83) further demonstrate promise of adjunct agents, notably clonidine and bupivacaine, in addition to IT morphine to produce chronic pain relief. These 2 studies were also able to report that IDDS with IT morphine was not only safe across a chronic time frame, but also that safety profiles were preserved with IT morphine admixed with other agents.

Chronic Unspecified Pain

Chronic unspecified pain has been thought of challenging to treat with IDDS (9,45,62). Nonetheless, much impactful research has shown promise of IT ziconotide more than other agents in being effective in this population (Table 3). This sentiment was elegantly demonstrated by the recent PRIZM study by Deer et al (85), which was comprised of a largely non-cancer pain cohort who either received IT ziconotide as a first-line agent or after failure of other IT agents. In this study, Deer et al (84) found that although both groups experienced analgesic benefit, those persons who received IT ziconotide as a first-line agent reported greater pain benefit. Similarly, Wallace et al (85) found that IT ziconotide was able to produce meaningful analgesic benefit and opioid reduction when used as an adjunct in persons with chronic pain refractory to IT morphine. Although largely well tolerated, practitioners must maintain a healthy cognizance of IT ziconotide-associated neuropsychiatric disturbances. Wallace et al (86) report their findings of these serious adverse effects being highly correlated with faster dose titration schedules.

Few prospective studies have also shown benefit and safety of other agents, largely IT morphine, in being effective for chronic nonmalignant pain. An interesting study by Veizi et al (87) also found that adjunct bupivacaine helps restrain IT morphine dose escalation within the first year. Rauck et al (88) in a well-designed, placebo-controlled, and double-blinded RCT using a large cohort (n = 170) found no benefit of IT gabapentin in producing analgesic benefit or reduction of opioids or opioid-specific adverse effects. Studies by Thimineur et al (89) and Anderson et al (90) are further demonstrative of intrathecal opiate therapy yielding decrement of chronic unspecified pain and improving functional outcomes in these patients.

Table 3. *Highest available evidence for use of IDDS in treating chronic non-cancer pain.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Wallace 2006 (85)	IT ziconotide	Refractory chronic pain, n = 255	RCT (DB-PC), I	Efficacy, adverse effects	6 days	IT ziconotide was effective in pain reduction, but rapid titration caused a lot of adverse effects.
Rauck 2013 (88)	IT gabapentin	Chronic non-cancer pain, n = 170	Multicenter, RCT (PC-DB), I	Pain, systemic opiate use, opiate adverse effects	22 days	IT gabapentin was as safe as oral gabapentin, but was not effective in reducing pain, systemic opiate use, or opiate adverse effects.
Deer 2018 (PRIZM) (84)	IT ziconotide as first vs. not-first IT agent	Chronic pain from cancer and non-cancer etiologies, n = 93 but only 4% had cancer-pain	Multicenter, prospective, II	Long-term safety, pain relief	12 months	IT ziconotide produced analgesic benefit in both groups, but had greater efficacy when initiated as first-line IT agent.
Veizi 2011 (87)	IT opiates vs. combo opiate + bupivacaine	Chronic non-cancer pain, n = 126	Retrospective cohort, III	Pain relief, opiate reduction, IT dosage escalation	12 months	IT opiates with adjunct IT bupivacaine blunted IT opiate escalation.
Wallace 2008 (86)	IT ziconotide as adjunct to IT morphine	Patients with suboptimal pain relief with IT morphine, n = 26	Multicenter, prospective, II	Pain relief, opiate reduction, adverse effects	18 months	Addition of IT ziconotide as adjunct to IT morphine produces further analgesic benefit and reduces oral opiate dosage.
Thimineur 2004 (89)	IT medications (various, opiate and nonopiate) vs. CMM	Chronic nonmalignant pain, n = 69	Prospective, II	Efficacy (pain relief, function), adverse effects	3 years	Patient with extremely severe chronic pain receive analgesic benefit with IT therapy, but overall pain still remains high.
Anderson 1999 (90)	IT morphine	Chronic refractory pain, n = 30	Prospective, II	Pain, function, adverse effects	24 months	Long-term IT morphine was safe, effective, and improved function.
Webster 2009 (74)	IT ziconotide across time	Chronic pain from cancer AND non-cancer, n = 78	Multicenter, prospective, II	Long-term safety, pain relief	36 months	Long-term IT ziconotide was safe, well tolerated, and produced sustained analgesia.

DB, double blinded; PC, placebo-controlled

Trunk Pain

Most of the literature for IDDS efficacy in trunk pain was explored in persons with refractory postherpetic neuralgia (62,91-93). Despite being limited in context there exists 3 well-designed RCTs to confer a high level of evidence (Table 4). Of note, all studies utilized IT methylprednisolone as cerebrospinal fluid (CSF) inflammation was considered a prevailing theory for this poorly understood pain phenomenon. Kotani et al (94) even found that IT methylprednisolone and lidocaine combination was effective in sustaining analgesia across a follow-up period of 96 months. Dureja et al (91) found that although IT midazolam or methylprednisolone each themselves conferred only a short-term benefit; the combination of these medications produced a chronic analgesic benefit across a 3-month timespan.

Intrathecal Medications

Efficacy

There currently exists only 2 U.S. Food and Drug Administration (FDA)-approved IT medications for chronic pain: morphine and ziconotide (45,94). These 2 medications carry the highest amount of evidenced-based support from well-designed studies and are the only first-line options recommended for both nociceptive and neuropathic pain by the latest Polyanalgesic Consensus Conference (PACC) guidelines (94). Of note, multiple other IT medications, such as anesthetics and opioids other than morphine, are readily utilized with good benefit (5,7,39-41,66,68-75,80,82,84-88,95-97) (Tables 5–8). The PACC guidelines include the use of these other medications as second-line options—either alone or in combination. Although IDDS

Table 4. *Highest available evidence for use of IDDS in treating chronic trunk pain.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Dureja 2010 (91)	Epidural methylprednisolone vs. IT midazolam vs. epidural + epidural methylprednisolone + IT midazolam	Refractory postherpetic neuralgia, n = 150	Multicenter RCT (DB), I	Analgesic efficacy	12 weeks	Efficacy of epidural methylprednisolone or IT midazolam was short term, whereas the combination of epidural methylprednisolone + IT midazolam provided sustained analgesia.
Kikuchi 1999 (92)	Epidural steroid injection vs. IT methylprednisolone	Refractory postherpetic neuralgia, n = 25	RCT, I	Analgesic efficacy	24 weeks	IT methylprednisolone was superior to epidural steroid injections for efficacy and decreased CSF level of IL8.
Kotani 2000 (93)	IT methylprednisolone + lidocaine vs. IT lidocaine vs. CMM	Refractory postherpetic neuralgia, n = 277	RCT (DB-PC), I	Analgesic efficacy, interleukin levels	96 months	Only combination IT methylprednisolone + lidocaine provided analgesia.

DB, double blinded; PC, placebo-controlled

provides targeted and localized medication delivery, IT medications can cause unfavorable adverse effects, which must therefore be strongly considered along with efficacy.

Chemical Composition

In addition to the existing efficacy-based evidence for IT analgesics, the pharmacokinetics and physiochemical characteristics of the different IT medications should also be considered to deliver either precise and localized or diffuse and widespread drug delivery. The greater an IT drug's relative hydrophilicity, the greater its (1) CSF flow-driven cephalad spread, (2) parenchymal penetration, and (3) IT half-life (94,96-101). As expected, the opposite holds true for relatively lipophilic medications. The degree of an IT drug's hydrophilicity is inversely related to its octanol/water partial coefficient. These 3 mentioned pharmacokinetic variables, along with complex bidirectional CSF flow dynamics, help govern IT resident times and CSF distribution patterns, which often help dictate IT drug-receptor exposure (99-102).

These pharmacokinetic parameters can also be advantageously utilized in accordance with strategic IT catheter tip positioning and drug flow concentrations—the volume and speed of drug delivery. To amplify localized and precise drug delivery to a target of interest, the concomitant placement of the IT catheter tip at an adjacent level and use of a relatively lipophilic medication can help deliver high drug concentrations to the targeted area. Drug delivery precision can be further enhanced by higher drug injectate concentrations and slower delivery rates; faster injectate delivery rates allow for further CSF spread. On the contrary, in cases in which pain generation is not as discrete, greater CSF distribution may be considered favorable. Thus more hydrophilic agents and faster injectate delivery rates will help increase CSF distribution, cephalad spread, and IT half-life.

Adverse Effects

Because IT medications are isolated to the IT space and smaller doses are utilized relative to their systemic counter parts, serious systemic adverse effects tend to be fewer. However, many common and serious adverse effects still occur, and thus require a healthy threshold of suspicion to appreciate (56,102). These medication-associated adverse effects can occur by virtue of the medication and/or dose itself or can be sequelae of device complications, including pump malfunction or catheter dysfunction, wherein the appropriate medication dosages are not delivered to the IT space. Therefore for any signs or symptoms or medication withdrawal or overdose, device complications must be considered and ruled out. Moreover, sources of human error, including those with pump programming and drug concentration, also exist and must be considered.

A majority of the complications of IT medications are largely similar to those that occur with their systemic counterparts, as seen in Table 2. However, it must be noted that drug-specific anaphylaxis can result with any of the listed IT medications, and thus must be ruled out in the trial phase. Last, adverse effect profiles are

Table 5. *Highest available evidence for use of IT anesthetics in treating chronic pain syndromes.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Deer 2002 (69)	Pre: IT opiate vs. Post: IT opiate + bupivacaine	Chronic pain, n = 109 (n = 25 with metastatic cancer pain of spine)	Retrospective, III	Pain relief, opiate reduction, satisfaction, doctor and emergency room visits	Mean 15 months	The use of IT bupivacaine as an adjunct provided greater analgesic benefit and reduction of oral opiate when added to IT opiate monotherapy.
Mercadente 2007 (70)	IT morphine + levobupivacaine	Refractory cancer pain, n = 55	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + levobupivacaine produced significant analgesia and opiate reduction, with safety.
Sjoberg 1991 (71) and Sjoberg 1994 (72)	IT morphine + bupivacaine 1994 study utilized a 1:10 morphine to bupivacaine ratio	Refractory cancer pain, n = 52	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + bupivacaine was safe and effective, a 1:10 ratio was deemed efficacious, but with bupivacaine adverse effects noted in almost half of patients.
Veizi 2011 (87)	IT opiates vs. combo opiate + bupivacaine	Chronic non-cancer pain, n = 126	Retrospective cohort, III	Pain relief, opiate reduction, IT dosage escalation	12 months	IT opiates with adjunct IT bupivacaine blunted IT opiate escalation.
Kanai 2019 (96)	0.5, 1.0, and 1.5 mg of IT bupivacaine at 1-week intervals	Chronic low back and lower extremity pain, n = 70	Prospective, II	Safety, efficacy	12 months	IT bupivacaine was safe and effective, with 1.0 mg as the optimal dose
Hayek 2016 (97)	IT hydromorphone + bupivacaine, via patient-controlled analgesia system	FBSS, n = 57	Retrospective, III	Pain relief, opiate reduction	24 months	Patient-controlled analgesia delivery of IT hydromorphone + bupivacaine was safe and effective; IT dose titration was noted across time.

FBSS, failed back surgery syndrome

thought to be more prevalent in settings of mixed IT drug administration.

Drug Delivery Systems

CSF Flow Dynamics

CSF flow passes posteriorly to the spinal cord as it leaves the foramen magnum and returns upward anterior to the spinal cord (95,99-101). Little is known about the rate of absorption and drug dispersion in the CSF. The current understanding of complex fluid dynamics with image-free systems suggests that CSF is a mixed system with little flow. Therefore drug administration may not be uniform and may be limited to the tip of the catheter (103-105). Consequently, dispersion of medications will depend on posture and static position while sleeping. Catheter placement depends on clinical judgement and consensus of placement of catheters. High cervical catheters may be more effective in having the site of action in the cervical dermatomes. Anatomic variants may also affect the distribution of medications in the CSF.

Different IDDS Devices

Currently, there are various intrathecal pumps available; only one pump is FDA-labeled for intrathecal ziconotide (94). Infusion pumps can be mainly differentiated into systems with continuous flow or variable flow. The driving mechanisms may include peristalsis, fluorocarbon propellant, osmotic pressure, piezoelectric disc benders, or the combination of osmotic pressure with an oscillating piston. Pump materials are similar with the pump shell being titanium and filling ports containing silicone.

Physical orientation of the filling and side ports are largely consistent, with differences in negative pressure or positive pressure confirmation strategies (94,106). Pump delivery mechanics include continuous flow propellant or programmable features (107). Propellant

Table 6. *Highest available evidence for use of IT ziconotide in treating chronic pain syndromes.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type, Level of Evidence	Primary Outcome Measures	Study Length	Key Findings
Staats 2004 (66)	IT ziconotide	Refractory cancer or AIDS pain, n = 105	Multicenter RCT (DB+PC), I	Pain relief	10–11 days	IT ziconotide produced significant analgesic benefit.
Wallace 2006 (85)	IT ziconotide	Refractory chronic pain, n = 255	RCT (DB-PC), I	Efficacy, adverse effects	6 days	IT ziconotide was effective in pain reduction, but rapid titration caused a lot of adverse effects.
Webster 2009 (74)	IT ziconotide across time	Chronic pain from cancer AND non-cancer, n = 78	Multicenter, prospective, II	Long-term safety, pain relief	36 months	Long-term IT ziconotide was safe, well tolerated, and produced sustained analgesia.
Dupoiron 2012 (72)	IT ziconotide + morphine, ropivacaine, clonidine	Refractory cancer pain, n = 77	Prospective, II	Pain relief	3 months	IT ziconotide in combination with other IT agents was safe and effective.
Wallace 2008 (73)	IT ziconotide across time	Cancer or AIDS pain, n = 644	Multicenter, prospective, II	Safety and tolerability	2 months median	Most adverse effects (prevalence of 99% in cohort) were mild or moderate.
Wallace 2008 (86)	IT ziconotide as adjunct to IT morphine	Patients with suboptimal pain relief with IT morphine, n = 26	Multicenter, prospective, II	Pain relief, opiate reduction, adverse effects	18 months	Addition of IT ziconotide as adjunct to IT morphine produces further analgesic benefit and reduces oral opiate dosage.
Deer 2018 (PRIZM) (84)	IT ziconotide as first vs. not-first IT agent	Chronic pain from cancer and non-cancer etiologies, n=93 but only 4% had cancer-pain	Multicenter, Prospective, II	Long-term safety, pain relief	12 months	IT ziconotide produced analgesic benefit in both groups, but had greater efficacy when initiated as first-line IT agent

DB, double blinded; PC, placebo-controlled

pumps (Codman 3000 and Medtronic Isomed) do not require batteries and deliver a continuous flow for the life of the pump. The programmable pumps require battery replacement, based on labeling, at a maximum of 5 to 7 years for the Medtronic Synchromed II (Medtronic, Minneapolis, MN) and maximum of 10 years for the Flowonix Prometra II (Flowonix, Mount Olive, NJ).

The programmable pump systems feature differences that deserve mention (94,106,107). The Medtronic Synchromed II system uses a peristaltic rotor system of internal tubing to deliver medication from the reservoir to the external catheter system (108). The Flowonix Prometra II pump employs a valve-gated bellow delivery mechanism (109). Each pump has the ability for patients to deliver patient-controlled dosing by using a patient-held programmer (Patient Therapy Manager or PTM for Medtronic and the Patient Therapy Controller or PTC by Flowonix). Both pumps support magnetic resonance imaging (MRI) conditional labeling, with the Medtronic pump up to 3 Tesla and the Prometra pump at 1.5 Tesla (107,110). Of note, both pumps require interrogation following a scan. For the Medtronic system, exposure to a magnetic field will create a motor stall, which typically resolves following removal of the magnet and can occur within 20 minutes to 2 hours, with a failure of motor stall recovery on rare occasions. For this reason, it is suggested to interrogate after the scan.

One has to remove all medication within the reservoir prior to exposure to the MRI scan in persons with the Flowonix Prometra I system (111-113). Exposure to the magnetic field will result in emptying of the reservoir contents into the patient. The Prometra II system remedied this concern with the flow activated valve (FAV) that is triggered when exposed to a magnetic field, blocking drug delivery from the reservoir to the patient after delivery of less than or equal to 10 µL (109). If the contents of the reservoir are expected to be

Table 7. *Highest available evidence for use of IT opiates in treating chronic pain syndromes.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type	Primary Outcome Measures	Study Length	Key Findings
Rauck 2003 (39)	IT morphine	Refractory cancer pain, n = 119	Multicenter, prospective, II	Pain relief, opiate reduction, opiate adverse effect reduction	Up to 16 months	IT morphine produced significant analgesia (> 50% reduction in pain) and reduction in systemic opiate intake.
Smith 2002 (40)	IT morphine vs. CMM	Refractory cancer pain, n = 142	Multicenter RCT, I	Pain relief, opiate adverse effect reduction	6 months	IT morphine produced significant analgesic benefit, reduction in systemic opiate adverse events, and interestingly, improvement in survival.
Deer 2002 (41)	Pre: IT opiate vs. Post: IT opiate + bupivacaine	Chronic pain, n = 109 (n = 25 with metastatic cancer pain of spine)	Retrospective, III	Pain relief, opiate reduction, satisfaction, doctor and emergency room visits	Mean 15 months	The use of IT bupivacaine as an adjunct provided greater analgesic benefit and reduction of oral opiate when added to IT opiate monotherapy.
Onofrio 1990 (68)	IT morphine	Pain from end-stage cancers (metastatic and terminal), n = 53	Prospective, II	Efficacy and safety	4 months	Long-term IT morphine analgesia was safe and effective.
Mercadente 2007 (69)	IT morphine + levobupivacaine	Refractory cancer pain, n = 55	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + levobupivacaine produced significant analgesia and opiate reduction, with safety.
Sjoberg 1991 (70) and Sjoberg 1994 (71)	IT morphine + bupivacaine 1994 study utilized a 1:10 morphine to bupivacaine ratio	Refractory cancer pain, n = 52	Prospective, II	Pain relief, opiate reduction	6 months or death	IT morphine + bupivacaine was safe and effective, a 1:10 ratio was deemed efficacious, but with bupivacaine adverse effects noted in almost half of patients.
Dupoiron 2012 (72)	IT ziconotide + morphine, ropivacaine, clonidine	Refractory cancer pain, n = 77	Prospective, II	Pain relief	3 months	IT ziconotide in combination with other IT agents was safe and effective.
Brogan 2015 (95)	IT patient-controlled analgesia, using various agents 91% received IT morphine or IT Dilaudid; 16% received IT ziconotide	Refractory cancer pain, n = 58	Prospective, II	Pain relief, opiate reduction	Mean 1.5 months	Patient-controlled analgesia of IT medications yielded high patient satisfaction and significant analgesic benefit
Roberts 2001 (98)	IT morphine	Chronic pain, N = 88 (major conditions including axial pain conditions n = 68)	Prospective, II	Efficacy (pain relief, function), adverse effects	Avg 36 months	Most patients had significant pain relief and satisfaction with IT morphine doses requiring titration across the 3-year period.
Deer 2004 (7)	IT morphine	Low back pain, n = 136	Prospective, II	Pain, quality of life	12 months	A majority of patients had significant reduction in back and leg pain, improvement in quality of life, and reported high satisfaction.
Winkelmuller 1996 (82)	IT morphine (+buprenorphine, clonidine, fentanyl, bupivacaine, or NaCl in various combinations)	FBSS, n = 120	Retrospective, III	Efficacy (pain relief, function), adverse effects	6 months, to 5.7 years max	A majority of patients reported analgesic benefit with high satisfaction.

FBSS, failed back surgery syndrome

Table 8. *Highest available evidence for use of nontraditional IT medications in treating chronic pain syndromes.*

Author, Year	Intervention	Patient Type, Sample Size	Study Type	Primary Outcome Measures	Study Length	Key Findings
Hassenbusch 2002 (75)	IT clonidine	Cancer pain refractory to previous IT therapy, n = 31	Prospective, II	Efficacy, tolerability	Mean 16 months	IT clonidine was safe and effective; approximately half of patients had long-term analgesic benefit.
Rauck 2013 (88)	IT gabapentin	Chronic non-cancer pain, n = 170	Multicenter, RCT (PC-DB), I	Pain, systemic opiate use, opiate adverse effects	22 days	IT gabapentin was as safe as oral gabapentin, but was not effective in reducing pain, systemic opiate use, or opiate adverse effects.
Munts 2009 (80)	IT glycine vs. saline solution	CRPS 1 with dystonia, n = 19	Double-blind crossover, I	Pain, dystonia	4 weeks	IT glycine did not produce any meaningful reduction in pain or dystonia.

DB, double blinded; PC, placebo-controlled

less than 1 mL, the medication should be removed prior to the MRI because the FAV may not activate. After the MRI, the contents of the reservoir have to be removed in entirety to manually reset the FAV, the pump interrogated and the contents replaced in sterile fashion, with elapsed time of 3 minutes. The Medtronic Synchromed II system has a minimal flow rate of 0.048 mL/day to allow for programming, whereas the Prometra II system can be at zero flow. Accuracy of the Prometra system is greater (97.8%) compared with the Medtronic Synchromed II system (2% vs. 14.5%).

The Medtronic system has 2 reservoir sizes, 20 and 40 mL, whereas the Prometra II system has a 20 mL reservoir and recently obtained FDA approval for a 40-mL device. Physical orientation of the filling and side ports are largely consistent, with differences in negative or positive pressure confirmation strategies. Pump delivery mechanics include continuous flow propellant or programmable features. Propellant pumps (Codman 3000 and Medtronic Isomed) do not require batteries and deliver a continuous flow for the life of the pump. The use of propellant pumps are very rare in current practice and have been utilized more commonly for infusion of intravascular chemotherapy for hepatic malignancies. The programmable pumps require battery replacement, based on labeling at a maximum of 5 to 7 years for the Medtronic Synchromed II and maximum of 10 years for the Flowonix Prometra II. The programmable pump systems feature differences that deserve mention. The Medtronic Synchromed II system uses a peristaltic rotor system of internal tubing to deliver medication from the reservoir to the external catheter system. The Flowonix Prometra II pump employs a valve-gated bellow delivery mechanism. Each pump has the ability for patients to deliver patient-controlled dosing by using a patient-held programmer (Patient Therapy Manager or PTM for Medtronic and the Patient Therapy Controller or PTC by Flowonix). Both pumps support MRI conditional labeling, with the Medtronic pump up to 3 Tesla and the Prometra pump at 1.5 Tesla. Of note, both pumps require interrogation following a scan. For the Medtronic system, exposure to a magnetic field will create a motor stall, which typically resolves following removal of the magnet and can occur within 20 minutes to 2 hours, with a failure of motor stall recovery on rare occasions. For this reason, it is suggested to interrogate after the scan. The Flowonix Prometra I system requires removal of all medication within the reservoir prior to MRI exposure, as failure can result in emptying of the reservoir contents into the patient. The Prometra II system may have remedied this concern with the FAV that is triggered when exposed to a magnetic field, blocking drug delivery from the reservoir to the patient after delivery of less than or equal to 10 L. If the contents of the reservoir are expected to be less than 1 mL, they should be removed prior to the MRI because the FAV may not activate and could in rare cases cause intrathecal drug overdose. Prior to the MRI, the contents of the reservoir have to be removed in entirety and then replaced after the imaging is complete. A fill and refill will manually reset the FAV, the pump interrogated, and the contents replaced in sterile fashion, with elapsed time of 3 minutes. The Medtronic Synchromed II system has a minimal flow rate of 0.048 mL/day to allow for programming, whereas the Prometra II system can be at zero flow. MRI scan recommendations have been revised for the Prometra pump and are available. Accuracy of the Prometra system is greater (97.8%) compared with the

Medtronic Synchromed II system (2% vs. 14.5%). The Medtronic system has 2 reservoir sizes, 20 and 40 mL, whereas the Prometra II system has a 20 mL reservoir only.

In 2015, the FDA identified several factors in the design of the Synchromed pump that had been addressed (108). The major factors were encapsulating the feed throughs with silicone to prevent motor stall, modified the gear material so it was less corrosive, reduced the infusion rate to prevent overinfusion by decreasing the amount of infusion, and applied a diamond-like coating to the motor shaft to reduce wear and motor stall. These factors then allowed the pump to comply with the FDA.

IDDS Trial

It has recently been studied that there are no essential differences in trialing methods. There are some cases that trialing is not needed before implantation. Anderson and Burchiel (90) found that in 37 patients with chronic nonmalignant pain randomized to continuous epidural or intrathecal injection, there was no difference in outcome after trialing these 2 different ways. They concluded that intrathecal injection was safe and less costly than continuous epidural infusions and had similar predictive value. A study from Dominguez et al (114) noted in 86 patients that a correlation may exist between the intrathecal trial dose of opioids to ultimate intrathecal dose requirements. However, there is currently no way to predict the amount of medication needed for analgesia during intrathecal infusion. The consensus of the PACC 2012 concluded that the use of a trial in chronic cancer pain is debatable. Nevertheless, many clinicians recommend a trial before implantation. The PACC has recommended a 50% reduction in pain, and a favorable side effect profile.

Many place intrathecal catheters at T9-T10 away from the conus. In some settings, such as head and neck pain or upper extremity pain focus, clinicians have placed catheters in the cervical region. The duration of the trials are variable. Anderson and Burchiel (90) data suggested that a single intrathecal injection may be effective and cheaper. Grider et al (42) in a retrospective review utilized low-dose intrathecal injection with good results. This study concluded that a 6-week opioid-free trial may help improve analgesia when compared with oral opioid and intrathecal drug combinations. Analgesia may be maintained at lower microgram doses. Opioid tolerance may be reversible in 6 weeks. In this review, a dose-response relationship of 400 mcg of intrathecal morphine was achieved (range 50–400 mcg/day). In conclusion, trialing for a short period of time is adequate, bolus trialing may save money and be effective, and patients who are less tolerant to opioids have more accurate trials.

Complications and Adverse Events

Complications associated with IDDS can be divided into several categories that include hardware malfunction complications, procedural-related complications, and medication-associated complications (56,102). Although the focus of our review is based on the treatment of pain with IDDS, literature from baclofen pump implantation is also useful when considering complications and adverse events associated with intrathecal drug delivery via pump. It should be noted that the comorbidities present in patients who undergo placement of IDDS for pain can be different that those patients with spasticity. Much of the evidence regarding complications and adverse events with IDDS for spasticity is from pediatric patients with cerebral palsy, who may be at risk for poor nutrition, wounds, and incontinence that impact their complication rates.

Mechanical Complications

Catheter-Related Complications

Catheter malfunction is one of the most common causes of complication in patients undergoing IDDS. Catheter complications can be categorized into problems with leakage or a break in the catheter, displacement or migration, and catheter to pump disconnection.

Catheter displacement occurs in 3.7% to 10.5% of patients (115,116). A prospective study by Follett and Naumann (117) reported catheter complications in 49 catheter systems (37 of 209 patients, 17.7%), and specified if the complication was owing to the catheter or procedure related. Complications due specifically to the catheter were in 7 patients (3.3%). The same study had 12 cases of catheter dislodgement/migration that interrupted drug delivery, 10 of which were interpreted as procedure-related complications. Anchoring the catheter can minimize migration, as they found that in 6 of the 10 catheters had not been anchored at implant. There were 6 of 13 catheters that migrated when not anchored (46.2%), compared with 6 of 222 catheters that were anchored (2.9%). The same study reported 5 catheter kinks related to either suture placement or positioning of

the catheter. Another study reported 6 catheter complications out of 23 patients, but did not distinguish between catheter leaking, kinking, or dislodgement (118). In the Flückiger et al (119) 2008 retrospective review of 100 patients who were followed for up to 12 years, 36 experienced catheter problems requiring replacement, including 11 dislocations at the catheter tip, 9 disconnections at the pump, 13 with catheter leakage, 2 with catheter occlusion, and one catheter-tip granuloma. The study reports that some of these catheter complications were avoidable due to surgical technique. New technology was also introduced in 2007, so data may not reflect actual practice today. Follett and Naumann (117) published a review of surgical practices associated with low catheter-related complication rates. These surgical practices include a mid-to-upper lumbar dural entry level, shallow-angle paramedian oblique insertion trajectory, and meticulous catheter anchoring and tunneling techniques.

Pump Malfunction

The remainder of pump malfunctions, including both mechanical failure of the pump or battery and pump rotor malfunction, are fairly rare. Borrini et al (120) reported pump dysfunction in one patient in a prospective observational cohort of 158 patients. In the Flückiger et al (119) review of 100 patients over a 12-year period there were 14 pump defects, but no specific details regarding the nature of pump defects. In the same study, pumps required replacement due to battery exhaustion at an average of 55 months. In a prospective study of 18 patients, a rotor stall occurred in one patient and 2 patients experienced battery exhaustion (121). It should be noted that magnetic fields can interfere with the functioning of an intrathecal pump and temporarily stop the rotor of the pump motor. A case report from 2012 in which a patient underwent multiple MRIs experienced 2 separate memory failures leading to withdrawal symptoms (121). Pump interrogation should be performed after MRIs to ensure detection and proper functioning of the pump (122).

Malpositioning of Pumps

Several studies cite pump-related problems with positioning, often leading to another surgery for revision. Hassenbusch et al (121) reported that 2 of 18 patients in his 1995 study required revision of the pump due to shifting in position over 6 to 12 months postimplant. In the Kumar et al (118) 2002 review, 5 patients required surgery for pump flipping of 23 patients. In the Rauck et al (112) 2010 review in morphine for treatment of intractable pain, one of 110 patients experienced flipping of the pump and 2 patients had pump migration. Motta and Antonello (123) reported that out of 430 patients, in 3 cases the pumps flipped over and in 1 case it spontaneously migrated into the intraperitoneal cavity. Two of these patients had the pump removed due to an adverse-related event, and in the other 2 patients the pump flipped and the event spontaneously resolved. Pump flipping remains a risk that can require additional surgical intervention, however, it remains rare and has not been associated with severe adverse events in the current literature. It is recommended that the pump pocket be minimally larger than the pump to prevent excessive movement and flipping.

Procedural Complications

Postdural Puncture Headache/CSF Leaks/Hygroma

Postdural puncture headaches, or meningeal puncture headaches, can occur after there has been disruption of the dura and arachnoid mater thought to affect CSF dynamics (124). Two case reports have been published in which patients with postdural puncture headaches received epidural blood patches for pain with complications, the first being Hustak et al (125) with a case of subarachnoid bleeding, and the second Magro et al (126) with a case of bilateral subacute subdural hematoma. CSF leaks typically present as subcutaneous swelling beneath the lumbar incision and/or around the pump. Follett and Naumann (117) reported 4 CSF leaks and associated spinal headaches occurring in 4 of 209 patients. The Motta and Antonello (123) retrospective study had a rate of 4.9% CSF leakage that required blood patches, whereas 38 other patients (9%) had CSF leakage that cleared spontaneously. Three cases (4.2%) required explantation due to chronic CSF leakage. Motta and Antonello (123) found that the rate of CSF leakage decreased after application of pressure dressings. CSF leaks can impair wound healing, be a nidus for infection, and cause pain. It is important to optimize surgical techniques to minimize CSF leakage by a single needle puncture at the appropriate angle with purse-string circumferential sutures (127).

Bleeding

Intrathecal therapy has been previously defined as a high- or a high-to-intermediate risk procedure

based on guidelines published by PACC (10,11). Bleeding can occur as an epidural hematoma, spinal hematoma, or pocket hematoma. The incidence of bleeding is low but can be a devastating complication. Warner et al (11) performed a retrospective single-center review from 2005 to 2014 of 216 adult patients undergoing IDDS implantation or revision in a total of 247 procedures and found no cases of bleeding-related neurologic complications, including patients receiving periprocedural ASA (16.6%), NSAIDs (12.6%), or both (3.2%). Three patients did receive a periprocedure red blood cell transfusion within 72 hours of the procedure. Two of these patients had received ASA 81 mg within 7 days of the procedure, and one had received perioperative ibuprofen therapy. They all had baseline anemia. There are rare case reports of spinal hematomas, including a case report by Hustak et al (125) in 2014 in which a patient who underwent 2 epidural blood patches for persistent meningeal puncture headache developed a symptomatic lumbar subarachnoid hematoma requiring laminectomy, hematoma evacuation, and IDDS explantation. The incidence of pocket hematomas is also unknown, however, there is an abundance of literature regarding pocket hematomas after implantable cardioverter defibrillator (ICD) implantation. When pocket hematomas are present after ICD implantation, Essebag et al (128) demonstrated that it is associated with a higher risk of infection, with infection occurring in 11% of patients with a clinically significant hematoma, compared with 1.5% of patients without a clinically significant hematoma. In the Sridhar et al (129) 2016 review of 85,276 primary ICD implantations, 2.6% were complications by a hematoma. Risk factors included increased age (>75 years), congestive heart failure, coagulopathy, and renal failure. Patients who developed a hematoma had longer hospitalizations and higher in-hospital costs, and hematoma formation did not adversely affect mortality.

Infection

Infection is a major complication of IDDS and can either occur at the site of the pump, a lumbar wound, or meningitis. Follet et al (130) elucidates that when considering infectious complications and associated risk factors, it is worthwhile to consider data from spinal cord stimulation and CSF shunts, as these procedures share many features with IDDS, including catheterization of the subarachnoid space with a connection to a system implanted subcutaneously. Extrapolation from other surgical site infection data also identify risk factors for surgical site infections, which include older age, diabetes mellitus, immune system disorders, limited mobility, and hospitalization. Olsen et al (131) identified risk factors for surgical site infection following orthopedic spinal surgeries, and found that diabetes was the highest independent risk of spinal surgical site infection, and even serum glucose levels preoperatively (> 125 mg/dL) and 5 days postsurgery (> 200 mg/dL) were significantly higher in patients with surgical site infections. Other studies suggest that infection rates varied from 2.5% to 9% (130). The highest infection rate was found in a randomized control trial by Kumar et al (118) in which 6 of 23 patients receiving intrathecal therapy developed infections. Four of these patients had superficial infections that improved with antibiotics and did not require explantation of the device. One patient required explantation of the device due to infection, and one patient developed meningitis after a catheter was replaced at another institution. In the Motta and Antonello (123) retrospective review of 430 patients over a 14-year period in patients receiving baclofen intrathecal therapy, 10% of patients with pump placement subcutaneously suffered from infections, however, only 3.6% patients with subfascial pump placement developed infections. Infections are typically diagnosed based on strong clinical suspicion; however, some studies also include culture data supporting evidence of infection. Existing culture data show that infection is most often associated with skin flora: Staphylococcus, followed by Enterococcus, Streptococcus, and yeast. Treatment includes antibiotic therapy, and possible explantation of the device, and/or surgical washout. Meningitis is a rare but serious complication associated with IDDS. In cases of meningitis or encephalitis the IDDS should be removed and patients should receive parenteral antibiotics. The use of vancomycin powder has gained in popularity to reduce the risk of surgical site infections. Lemans et al (132) performed a retrospective review of 853 patients to determine the efficacy of vancomycin powder and povidone-iodine irrigation in spinal surgery to reduce surgical site infections and found a significant reduction in both deep and superficial infections in instrumented spinal surgery. There continue to be ongoing trials to establish data regarding efficacy of vancomycin powder in reducing surgical site infections.

Pharmacologic Complications

Catheter-Tip Granuloma

Catheter-tip granulomas, or inflammatory masses, can be seen after patients receive chronic medications intrathecally. There are no controlled trials to date that assess formation of granulomas, however, much of what we know comes from case reports and retrospective analysis. Catheter-tip granulomas, although infrequent, can be devastating as they may result in permanent neurologic injury. Estimates of the incidence of catheter-tip granuloma are < 3% overall. A systemic review by Duarte et al (133) was published in 2012 to evaluate association between formation of catheter tip intrathecal inflammatory masses with opioid dose and/or concentration. Duarte et al (133) reviewed 17 articles, representing 24 patients, and found that opioid dose and concentration were significantly associated with the development of catheter-tip granulomas. Flow rate was not found to be significantly associated with the development of catheter-tip granulomas, nor was an association between catheter tip location and development of inflammatory masses. PACC developed a consensus article regarding catheter-tip granulomas in 2012 for diagnosis, detection and treatment (134). The PACC recommends that an imaging study be performed if the patient has loss of pain relief consistent with granuloma development or has significant changes in sensory, motor, or proprioceptive function. MRI is the gold standard for granuloma diagnosis. Depending on position and severity, treatment of granuloma can include switching the medication, changing concentration, moving the catheter, or surgery.

Refill Complications

During drug refill, practitioners take extra caution to ensure that complications do not arise. This should be a sterile procedure to prevent infection. A 16-year retrospective cohort study of patients with spasticity treated with an intrathecal baclofen pump evaluated rate of infection per puncture for baclofen pump refill (135). The infection rate at this university hospital was 0.6% after reviewing 340 follow-up episodes with pump refill procedures. Interrogation of the pump is performed to determine the anticipated quantity of medication that will be aspirated from the reservoir. If the port is difficulty to identify, ultrasound guidance can be used (136). Pump location, body habitus, and anatomic difference can all contribute to difficulty properly identifying the port. Ultrasound guidance can decrease pain from multiple needle sticks, decrease the risk of infection, and help prevent subcutaneous injection or pocket fill of the medication. If pocket fill were to occur, the patient should be monitored for overdose or withdrawal as this can lead to serious adverse events, including death (137,138).

Chronic Follow-Up

Having routine postoperative appointments at regular intervals is vital to optimizing outcomes for patients who receive IDDS. These encounters will allow physicians to manage any present complications, adjust medication requirements, and screen for potential adverse outcomes while allowing patients to report their experience and symptoms. Consistent, long-term follow-up will ideally minimize complications and increase patient satisfaction.

Monitoring postoperative opioid consumption is important in the long-term follow-up. Tracking the changes in intrathecal and oral opioid doses can aid physicians in evaluating how effective the pump therapy is for the patient.

Intrathecal Opioid Dose Changes

Numerous studies have shown that over the short- and long-term, the intrathecal opioid dose required to achieve satisfactory analgesia increased. Kumar et al (139) showed an increase from 1.11 to 3.1 mg/day after 6 months and to 7.42 mg/day at final follow-up (mean 29.14 months). Similarly, Rainov et al (83) showed an increase in mean intrathecal opioid dose from 1.2 to 5.1 mg/day at 24 months.

In a novel study, Duarte et al (140) explored the possibility of a potential saturation point at which increasing opioid doses begin to exhibit no increased effect. They demonstrated saturation kinetics, evidenced by the increases from 0.81 to 2.53 mg/day, 3.34 mg/day, and 3.51 mg/day after 2, 4, and 6 years, respectively (140). At long-term follow-up on the order of magnitude of multiple years, Atli et al (141) noted that intrathecal opioid administration increased from 6.5 to 12.2 mg/day over 3 years. Winkelmüller et al (82) showed an increase from an initial dose of 2.7 to 4.7 mg/day after an average follow-up duration of 3.4 years. Interestingly, a prospective study by Sommer et al (116) showed that at 3-year follow-up, the intrathecal dose remained unchanged. However, overall the literature suggests that the required dose for control of pain following IDDS implantation increases over time. More longitudinal research needs to be conducted to

establish a saturation point and a time point in which the required dose tapers off, if any exists.

Oral Opioid Dose Changes

Often, patients who are using IDDS will still require adjuvant oral opioid medications. However, following IDDS implantation, the required oral opioid doses typically downtrend. Hamza et al (43) showed a significant decrease in daily oral opioid consumption after intrathecal pump placement, decreasing from 128.9 mg morphine equivalent dose at baseline to 3.8 mg at 3 months. Atli et al (140) demonstrated a similar effect over a more extended time, with oral opioid consumption decreasing from 183.9 to 57.6 mg/day at 3-year follow-up. Herring et al (77) showed a significant decrease as well over approximately 4 years, at an average rate of 2.08% per month. With adjuvant ziconotide, that rate increased to 4.58% per month; without, it decreased to 1.51% per month. Intrathecal bupivacaine increased oral opioid intake (77).

Most of the evidence shows that after undergoing IDDS implantation, patients have decreased systemic opioid requirements. The systemic opioid intake should be closely monitored at regular intervals following implantation, in hopes of weaning medications, as appropriate, to deliver primary analgesia via IT medications.

Hypogonadism

Opioids can modulate the hypothalamic-pituitary-gonadal axis and consequently affect hormone levels, ultimately resulting in hypogonadotropic hypogonadism. This condition can lead to diminished sexual function and osteoporosis, among other things. A study conducted by Duarte et al (142) showed that of the 20 patients included who had received intrathecal opioid therapy, 85% had biochemical hypogonadism, indicated by low follicle-stimulating hormone (FSH)/luteinizing hormone (LH) levels and low testosterone. Endogenous opioids have an important role in LH secretion, so their administration can result in an abnormal regulation of hormonal secretion. In that same study, 50% of the patients had osteopenia and 21.4% had osteoporosis, as measured by bone mineral density (142). A causal link between hypogonadism and osteoporosis has not been firmly established, although there does seem to exist a correlation between the 2 conditions.

To screen for hypogonadism, physicians should check free testosterone, total testosterone, sex hormone-binding globulin, LH, and FSH. Checking these levels should be a routine measure at the start of IDDS therapy and for long-term follow-up.

Conclusions

IDDS have been demonstrated to be highly effective interventions in treating a plethora of chronic pain conditions in various patient populations. Largely, the success of IDDS is highly dependent on various considerations in practice patterns that are necessary to address across the spectrum of management. Appropriate patient selection and periprocedural management involves the screening of potential IDDS candidates using a rigorous selection criterion assessing for the risk of bleeding, opioid abuse, psychological comorbidities, and infection. These criteria allow practitioners to identify and correct parameters that may ultimately compromise the safety or efficacy of IDDS interventions. Ultimately, the efficacy of IDDS is highly reliant on medications utilized and pain conditions being targeted. Although only IT ziconotide and IT morphine are FDA approved for treating pain, various other medications both alone and in combination have been utilized with good benefit. Postprocedurally, it is instrumental to maintain a healthy index of suspicion for different complications and adverse events, any of which can lead to significant morbidity and/or mortality if unaddressed. In summary, IDDS has extensive high-level evidence supporting its use and efficacy, and safety profiles can be optimized with prudent and judicious adherence to the spectrum of considerations in practice management.

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