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Narrative review

Epidural and Intrathecal Drug Delivery Systems for Chronic Pain Management: Progress, Promises, and Challenges

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Abstract:

Millions of people worldwide suffer from chronic pain, which significantly impacts their quality of life. Managing chronic pain is often complex and time-consuming. In this narrative review, we explore the use of epidural and intrathecal drug delivery systems (EIDDS) as a solution for chronic pain management. The purpose of this review is to provide an overview of recent approaches in targeted implantable drug delivery systems for chronic pain management, including their long-term safety, efficacy, cost-effectiveness, risks, and future opportunities and challenges. The data was gathered through extensive research using MEDLINE, PubMed, and Google Scholar databases, including studies published until June 13, 2023. The visual analogue scale, Karnofsky Performance Status (KPS), respiration, and oxygen saturation in the group receiving drugs through a targeted implantable drug delivery system were significantly better than those in the group receiving conventionally administered analgesia in a study on patients with advanced cancer. Whereas in comparison to conventional treatment alone, the targeted implantable drug delivery system alone or in combination therapy exhibited some advantages or similar effects in reducing chronic pain during a 1-year follow-up in patients with chronic non-cancer pain. Implantable drug delivery systems are a promising new treatment option for chronic pain treatment. All forms of pain, including those that are still challenging to treat with traditional methods, can now be targeted with devices and treatments.

Keywords: Chronic pain; Intrathecal; epidural; implantable drug delivery systems, epidural and intrathecal drug delivery system, EIDDS

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1. Introduction

At least 10% which is around 780 million individuals worldwide suffer from chronic pain, which impacts a sizable section of the population. The prevalence increases up to 25% of people who live in developing nations, are suffering from chronic pain (1).

Up to 85% of people with chronic pain report having severe depression, which is a startling statistic that highlights the impact this ongoing physical struggle has on mental health (2). Even more concerning, there is a strong correlation between chronic pain and suicide risk. Research indicates an alarming increase in suicides associated with chronic pain, accounting for 10.2% of suicides in 2014. Notably, opioid overdose accounted for 16.2% of suicides involving chronic pain, underscoring the possibility of opioid usage as a coping method (3). The detrimental impacts go beyond the body. Patients with chronic pain commonly struggle with sleep disturbances, with nearly half of them reporting a substantial sleep deficit of 42 minutes each night. Their physical and mental health continue to deteriorate as a result of this

poor sleep, starting a vicious cycle. (4). Long-term effects of chronic pain on quality of life are evident, as it raises the risk of depression, suicide, opiate use, and sleep disturbance. It's a complicated problem that needs to be addressed in order to enhance the general health of millions of people worldwide (5).

Conventional treatments for chronic pain, such as Oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), opioids, antidepressants, antiseizure medications, and anxiolytics, can be effective for some patients. However, occasionally, they are less effective and have specific drawbacks (6). Due to the fact that chronic pain is a complex condition with a variety of underlying causes and that people respond differently to different treatments, one of the limitations of conventional treatments is their effectiveness. While these therapies can relieve pain for some patients, they may not work equally well for everyone. These types of treatments not only have variable efficacy but also frequently cause adverse consequences. For example, stomach ulcers and bleeding are gastrointestinal problems that can be brought on by oral NSAIDs. Opioids have a high risk of addiction, tolerance, and dependence, even though they are frequently recommended for severe pain. For instance, the opioid crisis in the US has brought attention to the possible risks associated with long-term opioid usage. While thinking about opioid medication for the treatment of chronic pain, it is important to carefully consider the advantages and disadvantages (7).

Furthermore, due to the drawbacks and dangers of conventional medicines, alternative therapeutic modalities are required. For example, targeted implanted drug delivery systems enable the localized distribution of analgesic drugs to the site of pain, which may minimize systemic adverse effects. Other treatment options, such as physical therapy, cognitive-behavioral therapy, and complementary and alternative medicine, may be more effective for more people who are not responsive to conventional therapies (8, 9).

The epidural and intrathecal drug delivery system (EIDDS) is a medical device that can be surgically inserted inside patient tissues to deliver a therapeutic substance and enhance its effectiveness and safety by managing the rate, timing, and location of drug release in the body (10). The importance of employing EIDDS for managing chronic pain is that they can offer a more reliable and controlled medicine delivery than traditional techniques, including oral tablets or injections. This may lessen pain flare-ups since these devices help overcome treatment compliance or adherence issues associated with conventional drug forms like oral drugs or injectables. Additionally, EIDDS can be designed to give medication at predetermined intervals or in reaction to specific events like changes in body temperature or level of activity (11, 12). Ensuring the patients take the appropriate dosage at the appropriate time can further enhance pain control. However, there are certain knowledge gaps regarding the application of EIDDS for the treatment of chronic pain. For instance, it is not yet known how long EIDDS can be used safely or what these devices' potential long-term negative effects are. In addition, some patients may find the cost of EIDDS to be prohibitive. Some risks may be faced during the treatment of chronic pain through this method, such as infection, drug toxicity, and other complications (13, 14). Therefore, this review will provide an overview of recent targeted implantable drug delivery system treatment approaches available for chronic pain management. Also, its long-term safety, efficacy, cost-effectiveness, risk, and future opportunities and challenges will be covered.

2. Method

According to published guidelines on narrative reviews, a review of studies looking into implantable drug delivery systems as a potential therapy option for managing chronic pain was conducted (10). The published paper to June 13, 2023, was manually searched on MEDLINE PubMed and Google Scholar. Pain, chronic pain, implanted drugs, opioids, epidural, intrathecal, cancer, and non-cancer were used in combination with free-text and MeSH terms. Studies that looked at methods for the treatment of chronic pain were chosen for inclusion. The search was limited to English-language articles only.

3. Neuroanatomy and physiology of the Epidural and Intrathecal Spaces for Targeted Drug Delivery

The dura mater, arachnoid mater, and pia mater protective membranes surround the spinal cord, which is suspended in a medium of cerebrospinal fluid (CSF) (15). The arachnoid mater is tightly adhered to the exterior, robust dura mater, while the pia mater covers the spinal cord. All three membranes are outside of the epidural space. Rich venous plexus, spinal arterioles, lymphatics, and extradural fat are all present in the epidural area. The CSF is located in the intrathecal space between the arachnoid and pia maters (16).

The 31 pairs of spinal nerves, each with an anterior and a posterior root, exit through the foramina between the vertebrae. Each spinal neuron supplies/innervates a particular portion of the skin's surface, known as a dermatome. The epidural space is the area outside the dura mater. Analgesics are injected into the epidural space during epidural analgesia. An indwelling catheter may be used to administer analgesics continuously or as a single injection (17).

The delivery of analgesic medications (such as those mentioned above) directly into the CSF in the intrathecal space is known as intrathecal analgesia. The subarachnoid space is another name for the intrathecal space. Since analgesics administered this way are about ten times more powerful than those administered into the epidural area, lesser doses and volumes may be needed (18).

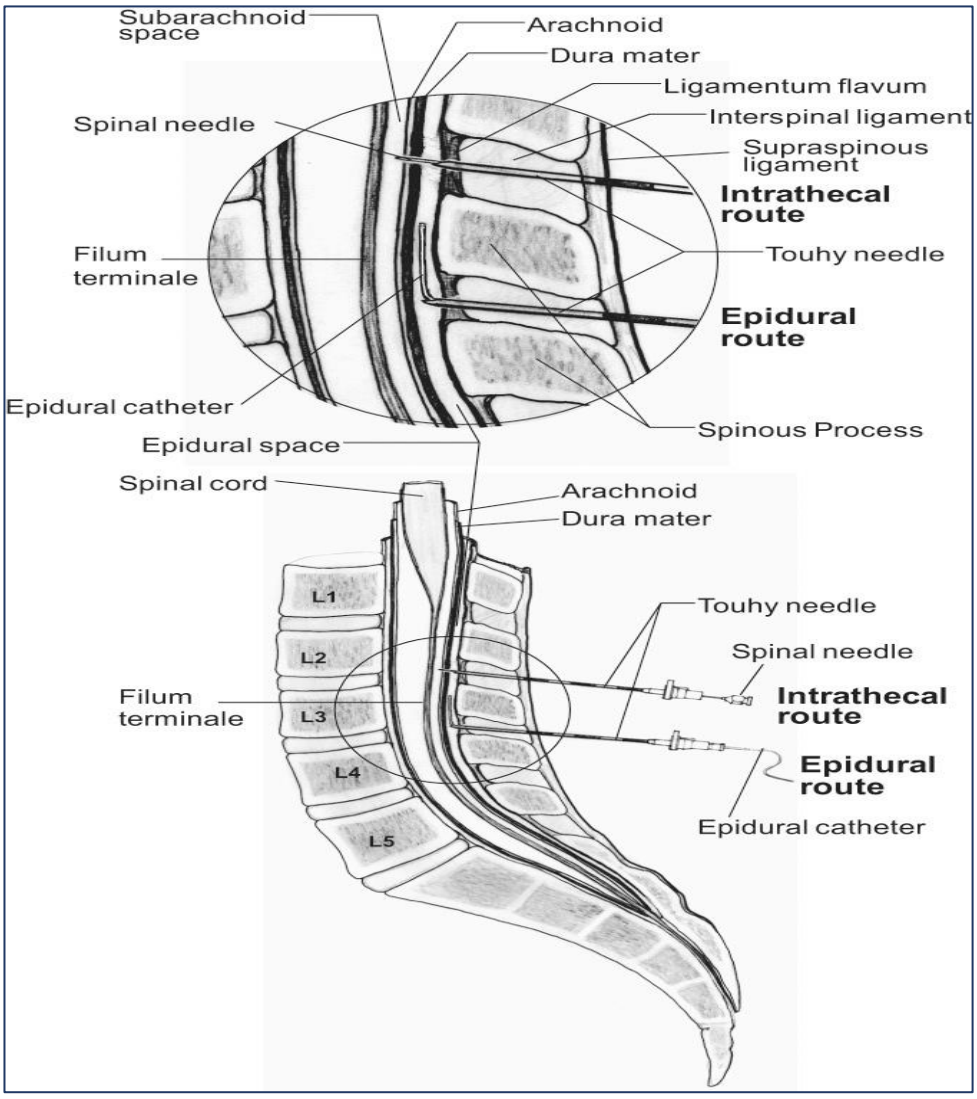

Figure 3 Gross anatomy of the spinal cord. Cox F (2009), Perioperative Pain Management, Wiley-Blackwell (16).

4. Indications and Patient Selection for EIDDS

Depending on the underlying cause of the pain, chronic pain can be divided into malignant and non-malignant categories. Cancer or another progressive disease is the source of malignant chronic pain, although non-malignant chronic pain can be brought on by several other conditions, including injury, inflammation, or nerve damage (19). Cancer and non-cancer-related pain are further subgroups of indications for the use of intrathecal or epidural medication delivery systems in the treatment of chronic pain. To properly treat cancer-related pain, patients may require substantial dosages of oral opioid medicines that are resistant to traditional medical therapy (20). Patients are vulnerable to systemic side effects of these drugs at such high dosages of oral opioids, which may include constipation, respiratory depression, and even death. Providing appropriate analgesia without causing systemic side effects and enhancing the quality of life may be achieved with intrathecal and epidural administration of opioids (21). Most people who are chosen for this pain treatment that is not cancer-related and typically have spine diseases as the cause of their pain. Compression fractures, spondylolisthesis, spondylosis, failed back surgery syndrome, and spinal stenosis are only a few examples of these diseases (22). Complex regional pain syndrome, pelvic pain, and abdominal pain are some other non-cancer-related pain syndromes that are being addressed by EIDDS since they are typically resistant to other treatment techniques (23).

The following are the standard selection criteria for patients who are qualified for intrathecal medication infusion pump implantation (24, 25):

1) A patient who has failed to respond to conservative treatment and has moderate to severe pain (VAS > 4).

2) A successful trial is generally considered to have a test phase that provides adequate pain control (>50% improvement for at least 10 hours is traditionally considered adequate), with manageable side effects, and 50% functional improvement (Implantable drug delivery for chronic pain management-scope, limitations, and future).

3) The patient's treatment response is subpar, and the usage of oral/transdermal medication causes unacceptably bad adverse effects.

4) The patient has a healthy spinal column that is suitable for the implantation of a spinal infusion system.

5) The patient must give informed consent, and no chronic hematologic problems or active infection would preclude implantation.

6) The patient has no skin conditions and no prior history of pharmacological or common infusion system component allergies.

7) The patient has no history of substance misuse (alcohol or drugs) and no psychiatric or psychological disorders that would rule out implantation.

5. Evidence bases for effectiveness in malignant and chronic non-malignant pain

a) Epidural and intrathecal drug delivery system for the management of chronic pain related to cancer

In 2018, 9.6 million people died from cancer, which is the second largest cause of death worldwide. 2 million individuals worldwide endure pain each day, and cancer pain is one of the most serious unaddressed public health issues (26). More than 70% of cancer patients with advanced illness experience pain. In patients with advanced cancer, the introduction of targeted implantable medication delivery devices significantly reduces systemic opioid consumption.

Recent research indicates that when compared to intravenously delivered analgesia, epidural implanted drug delivery systems had a greater incidence of chronic pain control and enhanced quality of life. The respiration and oxygen saturation in the group receiving epidural self-controlled analgesia (n = 26) were significantly better than those in the group receiving intravenous self-controlled analgesia (n = 24) in a study of 50 patients with advanced cancer. In the group receiving epidural self-controlled analgesia, the visual analog scale (VAS) was significantly lower than in the intravenous self-controlled analgesia group, and the Karnofsky score was significantly higher in the epidural self-controlled analgesia group than in the intravenous self-controlled analgesia group. Patients who received epidural self-controlled analgesia reported higher levels of satisfaction and fewer side effects than those who received intravenous self-controlled analgesia. In patients with advanced cancer, self-controlled epidural analgesia may significantly increase the quality of life and reduce discomfort (27).

From May 2014 to May 2018, Sindt, Jill E., et al. (28) performed a retrospective review of individuals who received EIDDS treatment for cancer pain. There were 173 patients in all, and 93% of them had stage IV illness. The median daily oral morphine equivalent (OME) before the implant was 240 mg (interquartile range: 130-390, range: 0-2616 mg). 57% of patients needed OME doses greater than 200 mg/day, and 19% needed doses greater than 500 mg/day. The interquartile range for the post-implant median OME was 0 mg (range 0-480 mg), and 82.6% of patients fully stopped using systemic opioids. Only 1.7% of patients used more than 200 mg of OME, whereas 11.0% of patients used less than 100 mg. Following EIDDS implantation, the mean OME was reduced by 94% (p 0.0001), and all patients who continued to use systemic opioids needed less OME than they had before the implantation. The authors conclude from their finding that implantation was linked to a considerable decrease in systemic opioid use 30 days after surgery in the largest cohort of patients with advanced cancer and refractory pain treated with EIDDS, with the vast majority of patients quitting systemic opioids. Patients who kept taking systemic opioids had lower levels of pain control than those who are implanted.

When the conventional WHO strategy has failed to adequately treat a patient's cancer pain, intrathecal medication administration is effective. Using the Brief Pain Inventory, Abdelemam, Rania M., et al (29) compared the level of pain relief in 22 patients between 2008 and 2013 before and after the placement of an intrathecal medication delivery system. They noticed a clinically and statistically substantial improvement in their pain right away. The average pain score on the Brief Pain Inventory decreased from 6.8 to 3.0 one week after insertion. Over six months, there was continued improvement in the pain scores. The authors conclude their case study that patients with difficult-to-control cancer pain can benefit from efficient pain treatment for several months with the proper use of intrathecal implantable medication delivery devices.

Intrathecal or epidural medication delivery systems have adequate and better pain management even when cancer has gone to an advanced stage. From 2013 to 2017, Streans, Sita M., et al (30)conducted a prospective, long-term, multicenter cohort study on 1141 cancer patients. According to the patient report, intrathecal implantable drug delivery systems can effectively and efficiently manage cancer patients' pain, even in more advanced stages of the disease, while simultaneously preserving their quality of life. The EuroQol with 5 dimensions (EuroQol-5D) scores within the cohort of patients who provided baseline and follow-up data significantly improved at 6 (P =.0007; n = 103) and 12 (P =.0026; n = 55) months compared to baseline, with significant improvement at 6 months (P =.0016; n = 41). 3.2% of patients had infections that required surgical treatment (IDDS explant, replacement, pocket revision, irrigation and debridement, etc.). According to the authors, this large-scale, multicenter, single-group cohort study adds to the body of previous RCT data that supports EIDDS as a secure and efficient therapeutic option with a favorable benefit-risk balance for the management of cancer pain. But this research was done on a single group of population without comparator and most patients presented were treated at a single center in the United States even if it uses large numbers of patients.

A Wilcoxon Signed-Rank test was used on 160 patients to assess the degree of pain relief, efficacy, and safety of patients who underwent EIDDS implantation at a multidisciplinary pain clinic. The charts of the patient's demographics, cancer type, and pain scores were

reviewed retrospectively. According to this retrospective review study, EIDDS can reduce cancer pain in a range of individuals, and it should be strongly examined as a treatment option for people whose cancer pain is unmanageable with conventional medical treatment(31). At the time of implantation, the median pain score was 7.1, and one month later, it was 5.0. The median reduction in pain was 2.5 for those who had baseline and one-month pain scores available (p 0.0001). Three months after implantation, pain assessments did not significantly change from those at one month. The median lifespan was 65 days. Since this research used a retrospective study design, the majority of the data came from doctor notes, which frequently lacked all of the relevant criteria. Additionally, there were no defined means for gathering chart data, such as pain scores, which could have indicated the patient's current suffering, average pain, or maximal agony. Due to the institution's extensive referral network and the fact that many patients obtained additional care nearby, follow-up statistics were limited. Even if those limitations are present there is insufficient evidence to support additional randomized trials comparing EIDDS to conventional medical management, despite the well-established advantage of EIDDS for the treatment of cancer pain.

Compared to comprehensive medical management alone, another randomized clinical trial using targeted implantable drug delivery systems with comprehensive medical management demonstrated superior clinical outcomes at 4, and 12 weeks for cancer treatment. In comparison to non-IDDS patients, the EIDDS VAS pain scores dropped by 60% at 4 weeks (P = 0.002) as opposed to 37%. In comparison to the non-IDDS group, the IDDS VAS pain scores had declined by 42% after 12 weeks, whereas they had decreased by 47% (P = 0.23). When CMM patients switched over and received EIDDS implants, the most resistant group, they experienced pain VAS reductions of 27%, which were clinically and statistically significant. EIDDS boosted cancer patient survival, increased therapeutic success, decreased pain scores, and alleviated most drug toxicity (21).

Overall, studies have indicated that epidural and intrathecal implantable drug delivery systems provide better pain relief and enhanced quality of life compared to conventional methods. These systems have been found effective even in advanced stages of cancer, with a substantial decrease in systemic opioid use and improved pain management. The use of implantable medication delivery systems, along with comprehensive medical management, has demonstrated superior clinical outcomes, including reduced pain scores and improved therapeutic success. Further research and randomized trials are needed to explore the full potential of these systems and compare them to conventional approaches

b) Epidural and intrathecal drug delivery system for the management of chronic pain related to non-cancer

Pain that generally lasts longer than six months in a patient who does not have cancer is referred to as chronic non-malignant pain. An essential element of interventional methods for refractory chronic pain disorders is implantable medication delivery systems. When compared to systemic opioid administration, continuous intrathecal or epidural opioid injection leads to higher subarachnoid drug concentrations, better pain scores, and fewer adverse effects (32). One international multicenter randomized, double-blind crossover study has shown that for chronic non-cancer patients, intermittent bolus infusion and continuous infusion have nearly comparable pain-controlling abilities, after the patients are implanted with a programmable intrathecal drug delivery (ITDD) device, either of intermittent boluses or a simple continuous flow in period 1, followed by a crossover to the alternative mode of administration, Eldabe, Sam., at al found that there is no significant difference in the Patients' Global Impression of Change (PGIC) scale. The authors came to this conclusion based on their observation that intermittent bolus dosing did not significantly alter the mean PGIC or the proportion of positive responders, and both ways of administration have significantly improved in controlling chronic pain than traditional or conventional ways of administration (33). In another study conducted to treat severe intractable chronic non-malignant pain, Hamza, Meged, et al (34)compared intrathecal boluses to continuous infusion trialing approaches before and after the implantation of drug delivery devices. Throughout the observation period, authors observed a statistically significant decrease in pain and an increase in function in both cohorts after DDS (drug delivery system) implantation. The overall limited dose escalation also applied to the IT dose, which remained almost stable throughout. There

was a considerable decline in oral opioid consumption. Between the two cohorts, there was no statistically significant difference in the prediction of trial success or long-term results. From this prospective, randomized, side-by-side, long-term study the authors conclude that intrathecal opioids with a drug delivery system at low doses can significantly and sustainably reduce pain in patients with chronic non-cancerous pain and improve function (physical and behavioral).

However, other writers, like Hayes et al. (35), challenge the risk/benefit ratio in patients with persistent non-malignant pain due to inconsistencies in the administration of intrathecal medication infusion in these individuals. They discovered that the use of IDDS (intrathecal drug delivery system) was of minor analgesic effect in the first 6 months of therapy, which was reduced over the longer term in their case-control research on 25 patients. They also saw a constant lack of functional improvement throughout IT therapy, a pattern of inactivity concerning self-management, and a considerable reinforcement of the sickness role. Adverse effects and dose escalation were frequently used on these patients. 24 out of 25 patients stopped receiving IT therapy, with 7 (29%) having urgent IDDS-related problems, 16 (67%) transitioning to oral/transdermal administration electively, and 1 due to a death unrelated to IDDS. Reduced physical activity, temporary withdrawal symptoms, and greater pain were all negative effects of stopping the medication. Contrarily, patient-reported benefits following the end of opioid infusion included fewer side effects (sweating, weight gain, and edema), the discontinuation of testosterone replacement therapy in some cases, increased comfort due to the disappearance of the abdominal mass effect brought on by the infusion device, and reduced hospital dependence due to fewer follow-up visits to the pain unit.

There is also another retrospective cohort study that shows that there is no significant difference in opioid consumption between patients who took conventional and implantable delivery systems in 6 months of treatment. From a total of 82 patients, the 12-month average morphine equivalents daily dosages (MEDD, mg/day) was considerably lower in the IDDS group compared to the comprehensive medical management (CMM) group (53.2 46.3 vs 123.9 176.4, respectively; P = 0.008), even though the 6-month average MEDD did not reach statistical significance. At baseline, ER visits were more common in the IDDS group than the CMM group (5.4 vs 0.5, respectively; P =.002), and this difference persisted for 12 months (P 0.001). Other than that, there was no difference between the groups during 12 months in the frequency of hospitalizations and medical costs for pain management. The authors conclude from their findings in comparison to CMM alone, the combination IDDS therapy exhibited some advantages in reducing opioid intake during a 1-year follow-up in patients with chronic non-cancer pain (36).

In general, studies have demonstrated that continuous intrathecal or epidural opioid injection leads to higher drug concentrations, improved pain scores, and fewer adverse effects compared to systemic opioid administration. The use of programmable ITDD devices, whether through intermittent bolus infusion or continuous infusion, has shown comparable pain control abilities. Implantation of drug delivery devices has been associated with a significant decrease in pain, increased function, and reduced oral opioid consumption. However, some researchers challenge the risk/benefit ratio of intrathecal medication infusion, citing inconsistent analgesic effects and limited functional improvement.

c) Epidural versus intrathecal implantable drug delivery system

Patients with neuropathic chronic pain, frequently brought on by spinal cord injury, are the main population for which intrathecal and epidural medication delivery systems are used. These techniques rely on implanting a pump/reservoir in a subcutaneous pocket under radiological guidance (37).

One well-designed trial demonstrates that, in cancer patients undergoing gastrectomy surgery, single-dose epidural opiates are more effective at reducing hospital stays than single-dose intrathecal opiates. The opioid consumption at 12, 24, and 48 h postoperatively was significantly lower in the thoracic epidural analgesia group than in the intrathecal morphine group at all time points, according to Desjardins, Philippe et al.'s (38) analysis of 79 patients who underwent gastrectomy for cancer from 2007 to 2018 over 11 years. At all-time points,

the intrathecal morphine group had a higher pain numeric rating scale score than the thoracic epidural analgesia group did. However, another similar study was carried out between July 2020 and June 2021 on fourteen patients who underwent pancreatoduodenectomy through an upper midline incision for neoplastic or pre-neoplastic illness. They conclude that epidural and intrathecal implanted drug delivery systems' baseline features did not differ statistically significantly from one another (39). However, further study is needed since the available studies on this topic are very limited.

6. Drugs used in epidural and intrathecal drug delivery for chronic pain

Epidural and intrathecal drug delivery (EIDD) aims to reduce the dose and adverse effects of the drugs by bringing them close to the receptors that affect pain modulation (40). The introduction of permanent intrathecal and epidural catheter implantation, along with internal or external ports, reservoirs, and programmable pumps, marked the beginning of intrathecal drug delivery (41).

EIDD is an effective medication for cancer patients with pain that won't go away. Patients with pain unrelated to cancer should only be given the choice of EIDD after exhausting all other treatment alternatives, such as spinal cord stimulation. The United States Food and Drug Delivery has only licensed morphine and ziconotide as monotherapies for EIDD delivery for the treatment of chronic pain. Off-label pharmaceutical use and combination therapy for pain management are frequently documented (42).

Neuropathic, nociceptive, and mixed pain were each given their level of proof, according to the PACC 2017. In general, ziconotide, opioid plus local anesthetic, local anesthetic alone, clonidine plus opioid, and clonidine alone are effective treatments for neuropathic pain. Opioids, ziconotide, opioids plus local anesthetic, and local anesthetic alone are typically effective treatments for nociceptive pain. Cancer pain (localized and diffuse) is divided into two categories by PACC 2017: non-cancer pain (localized and diffuse) is also divided into two by PACC 2017. The PACC 2017 recommendations for cancer and non-cancer pain are shown in the following table

Table 1 Medication-selection recommendations and considerations for targeted implantable (intrathecal)drug delivery system (43)

Levels	Cancer or Other Terminal Condition-Related Pain with Localized Nociceptive or Neuropathic Pain.
Line 1A	Ziconotide and Morphine
Level 1B	Fentanyl Morphine or fentanyl + bupivacaine
Level 2	Hydromorphone, Hydromorphone + bupivacaine, Hydromorphone or fentanyl or morphine + clonidine Morphine or hydromorphone or fentanyl + ziconotide
Level 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine, Ziconotide + bupivacaine Ziconotide + clonidine Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide Sufentanil
Level 4	Sufentanil + ziconotide Sufentanil + bupivacaine Baclofen Sufentanil + clonidine Bupivacaine + clonidine + ziconotide Bupivacaine + clonidine
Level 5	Sufentanil + bupivacaine = clonidine
Level 6	Opioid* + bupivacaine + clonidine + adjuvants

	Cancer or Other Terminal Condition-Related Pain with Diffuse Nociceptive or Neuropathic Pain
Line 1A	Ziconotide, Morphine
Level 1B	Hydromorphone, Morphine or hydromorphone + bupivacaine
Level 2	Hydromorphone or morphine + clonidine, Morphine or hydromorphone + ziconotide
Level 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine Ziconotide + bupivacaine, Ziconotide + clonidine, Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide Sufentanil
Level 4	Sufentanil + ziconotide Baclofen, Sufentanil + bupivacaine, Sufentanil + clonidine Bupivacaine + clonidine + ziconotide Bupivacaine + clonidine
Level 5	Sufentanil + bupivacaine + clonidine, Sufentanil + bupivacaine + ziconotide, Sufentanil + clonidine + ziconotide
Level 6	Opioid* bupivacaine + clonidine + adjuvants
	Noncancer-related pain with Localized Nociceptive or Neuropathic Pain
Line 1A	Ziconotide, Morphine
Level 1B	Fentanyl, Fentanyl + bupivacaine
Level 2	Fentanyl + clonidine Hydromorphone or morphine + bupivacaine Fentanyl + bupivacaine + clonidine Bupivacaine
Level 3	Fentanyl + ziconotide + bupivacaine, Morphine or hydromorphone + clonidine, Ziconotide + clonidine or bupivacaine or both Bupivacaine + clonidine
Level 4	Sufentanil + bupivacaine or clonidine Baclofen, Bupivacaine + clonidine + ziconotide
Level 5	Sufentanil + bupivacaine + clonidine Sufentanil + ziconotide
	Noncancer-Related Pain with Diffuse Nociceptive or Neuropathic Pain
Line 1A	Morphine, Ziconotide*
Level 1B	Hydromorphone, Morphine or hydromorphone + bupivacaine
Level 2	Hydromorphone or morphine + clonidine Fentanyl + bupivacaine, Ziconotide + morphine or hydromorphone
Level 3	Hydromorphone or morphine + bupivacaine + clonidine, Fentanyl + ziconotide, Sufentanil + bupivacaine or clonidine, Ziconotide + clonidine or bupivacaine or both
Level 4	Fentanyl or sufentanil + bupivacaine + clonidine Sufentanil + ziconotide Baclofen
Level 5	Opioid* + ziconotide + bupivacaine or clonidine

- Ziconotide* should be the first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of a history of psychosis,

- Opioid* (all known intrathecal opioids).

7. Cost-effectiveness of epidural and intrathecal delivery systems for chronic pain management

According to estimates, 43% of people have chronic pain, which places a big strain on their health and significantly lowers their quality of life when it comes to their health. As chronic pain is the second most frequent reason for requesting disability benefits, the financial burden is also considerable due to costs for medication, doctor visits, and other related expenses(44).

EIDDS are not only effective but also cost-effective, with Brogan et al. (45) demonstrating that the break-even point for IDDS for the management of refractory cancer pain occurs after six months of use due to lower drug expenditures and shorter hospital stays. Additionally, it was shown that IDDS therapy costs stabilized while those of traditional treatments continued to rise. Similar to this, Stearns et al. (30), using the Truven Health Market Scan Commercial Claims and Encounters Database, demonstrated that at 12 months, pharmacy costs were $9,264 higher for EIDDS while medical costs were $12,459 lower compared to conventional medical management (CMM), resulting in a total cost savings of $3,195 for EIDDS. The authors demonstrated more than $63,000 in cost savings after 12 months and more than $15,000 after two months of therapy with IDDS (rational) using the same database with more recent data (46), which covered the period from January 1, 2013, to September 30, 2019.

8. Complication

Although an implantable drug delivery system is a well-established method for treating chronic, severe pain, its dangers and side effects are just now starting to be more fully understood. The following are some of the complications of epidural and intrathecal drug delivery systems when we use them in the management of chronic pain (47-49):

Infection; The most severe complication, which may result in meningitis, an epidural abscess, or an infection of the spinal cord. Patients with a weakened immune system or those who have undergone prior spinal surgery are more likely to get an infection.

Bleeding; The use of anticoagulants, vascular lesions, inadequate hemostasis, and subsequent bleeding are all causes of bleeding. Swelling, pressure, and pain might result from bleeding with hematoma formation near the pump's insertion. Rapid action is necessary to address this issue.

Nerve damage; This could happen during the first surgery or afterward if the catheter kinks or is damaged. Pain, a lack of strength, numbness, or paralysis can result from nerve injury.

Overdose; This could happen if the patient unintentionally takes the pump's top off or if the pump has been improperly programmed. An overdose may result in coma, death, or respiratory depression.

Under dose; This could happen if the pump is improperly programmed or if the catheter is clogged. Pain, withdrawal symptoms, or other drug adverse effects may result from an under dose.

Device malfunctioning; If the pump or catheter isn't working properly, the drug may leak, cease working, or be administered in the incorrect amount. If a device problem is not identified and fixed, it could be fatal.

Additionally, allergic responses to the medication, headaches, nausea, and vomiting, dizziness, constipation, urinary retention, and skin irritation at the pump site are all potential side effects of epidural and intrathecal drug delivery systems. It is crucial to remember that these are just a few of the potential issues with intrathecal and epidural drug delivery systems.

Depending on the patient's unique characteristics and the exact conditions, the risk of each given problem will change(50).

9. Systems of epidural and intrathecal through an epidural or intrathecal delivery system

External system; This method consists of a tiny pump that is worn externally and a catheter that is inserted into the intrathecal or epidural area. When necessary, medication is replenished into the pump, and the rate of delivery can be changed. (50).

Implanted system; This device consists of a catheter that is inserted into the epidural or intrathecal space and a pump that is implanted under the skin. Through a port that is accessed through the skin, the pump is replenished with medication. A remote control can be used to change the delivery speed(51). The system used will rely on the specific requirements and preferences of the patient. External pump devices can be utilized for short-term treatment and are less intrusive. Fully implantable pump systems are more invasive, but they have the benefit of allowing the delivery rate to be changed without a trip to the doctor(52).

10. Implantation technique

The choice to place a pump is a complicated medical issue that needs thorough analysis, appropriate planning, and technical expertise. An implantation effectiveness test of the selected medication should be carried out before implanting an infusion pump (51). In the surgical room, the system must be implanted using strict aseptic procedures. Spinal anesthesia, regional anesthesia, or local anesthetic plus sedation are all options for doing the surgery. In some instances, general anesthesia will be used to carry out the procedure. Pulse oximetry, capnography, continuous ECG, and noninvasive blood pressure should all be used to monitor the patient as per normal practice. A prophylactic antibiotic should be given about 30 minutes before the procedure; our protocol calls for the intravenous administration of 2 g of cefazolin (50).

a) Intrathecal drug delivery system implantation method

Many people who experience chronic pain or suffer from cancer may find an intrathecal medication delivery device (pain pump) to be a wonderful, safe choice. There are far fewer side effects and reduced medication needs because the medicine is administered directly into the spinal fluid. A reservoir of medicine is implanted to supply at least one month's worth of treatment (40).

To place the catheter in the afflicted area of the spine, the providers make a small incision in the back. The real pump is then placed in the belly after an extension catheter is inserted under the skin from the spine around the torso. To ascertain whether the drug is efficient and whether a permanent pump is necessary, a trial intrathecal injection or temporary intrathecal pump is typically conducted. A catheter is used to administer the medication to the area surrounding the spinal cord, and the intrathecal pump itself is made of a metal pump that stores and delivers the medication. The drug can be delivered by the pump at various intervals during the day or with a slow release over some time (53).

b) Epidural drug delivery system implantation technique

Either the paramedian or midline approaches can be used to implant the epidural needle. In both situations, 1% lidocaine is injected into the region where the epidural needle is inserted. The needle is positioned in the midline between two spine processes when using the midline approach technique (54). The paramedian approach technique involves inserting the needle 1 cm laterally and 1 cm caudally from the lower border of the upper spinous process. Ligaments and soft tissue are penetrated with the epidural needle. The loss of resistance (LOR) syringe is used to locate the epidural space (55). By moving the needle attached to the syringe forward and pulling its plunger until the resistance is gone after the epidural space is reached, the syringe is filled with normal saline or air, and the resistance is measured. The LOR syringe is removed once the catheter is in the epidural space, and the epidural needle is then used to implant the catheter. Medication will be given by bolus or infusion using the catheter (56).

11. Patient satisfaction with EIDDS

The treatment of patients with persistent pain frequently involves targeted implantable drug delivery systems. The effectiveness of pain treatment, the decrease in opioid use, and the cost-efficiency of long-term pain management have all been demonstrated in previous studies. There aren't many studies looking at patient satisfaction with implanted pain pumps that are treated with specific intrathecal medicines (57).

One single-center survey study by Schultz, David M., et al. (58)shows that most patients reported improvements in their quality of life, physical function, and pain, as well as a decrease in their use of opioids after they started to use EIDDS. It was reported that 38.9% of patients had completely stopped taking oral opioids and continued taking only the EIDDS method. The position of the pump pocket was favorable to 91% of patients who were on the upper buttock pocket site overall. A viable option for long-term oral or skin patch opioid management, intrathecal TDD therapy can reduce pain and enhance the quality of life in patients with intractable pain. This research generally shows that patients with EIDD therapy express high levels of satisfaction. The clinical prognosis of individuals with complex chronic benign pain is still improved with intrathecal TDD treatment. Events involving mechanical failure, ineffectiveness, or the existence of comorbidities are factors that affect patient satisfaction. Quantifying the degree of improvements linked to the usage of TIDD therapy will require larger investigations in the future (59).

Another qualitative investigation on the effectiveness of implanted intrathecal pumps for chronic cancer-related pain was conducted by Hawley et al. (60). Six patients who also completed daily written questionnaires on pain and symptom management and perceived quality of life participated in a series of three semi-structured interviews. To determine the effect that caring for these patients had on the staff in a palliative care unit, interviews with nurses and doctors who were directly involved in the patients' care were also conducted. Even though their aspirations and expectations were not always fully realized, patients reported a significant decrease in their pain that had a profoundly good impact on their quality of life. Patients also indicated significant anxiety about relying on the gadget and a limited number of highly qualified people. The palliative care unit employees acknowledged that they had a big influence on the 'culture' of the facility. Both continual infusion management education and clear communication about the justification of the infusion were crucial. Following the intrathecal infusion, patients also needed continued palliative care to treat the mental, spiritual, emotional, and psychological components of their pain that were not controlled by it.

12. Challenges and Opportunities

a) Regulatory challenges for epidural and intrathecal delivery systems

The creation of novel EIDDSs that combine various technologies and medications has seen a fast surge in recent decades, with evident advantages. However, these goods pose an exceptional challenge for any health regulatory authority, including the US FDA, because of the novelty of these EIDDSs and the difficulty in determining the principal therapeutic benefit of such drugs(47).

The primary explanation is that health regulatory organizations categorize EIDDSs in various ways depending on the legal definition provided in the legislation they adhere to. Therefore, producers or sponsors cannot proactively foresee the regulatory classification of EIDDSs that combine multiple entities that are each designated as a medicine, biological product, or medical device. As a result, it might be difficult for manufacturers or sponsors to decide which regulatory channel they should use to distribute their EIDDS goods to clients (61). All regulatory processes are created to guarantee the effectiveness, safety, and caliber of products. Before granting the marketing approval, the developer should take these steps, such as determining the types of clinical and nonclinical trials necessary and the post-marketing quality standard requirements, such as Quality Systems for medical devices, current Good Manufacturing Practices for drugs, or both, such as the FDA's streamlined approaches for combination products.

Once more, the diversity of EIDDSs and the difficulty in determining the product's classification restrict the implementation of a single quality standard for all EIDDS products (62). Each EIDDS has unique requirements based on its purpose, intended application, and materials, pharmaceuticals, or biologics it contains; nonetheless, because all EIDDSs are administered parenterally, they must adhere to the quality control standards that apply to parenteral goods. The federal regulatory code has designated a few tools to assist developers in determining the quality testing necessary for their products. However, because the OCP has the final say in how combination products are categorized generally, a sponsor, manufacturer, or developer must have an early conversation with the OCP and the FDA's centers to get support and feedback for the creation of any EIDDS. Any sponsor or producer must be aware of the applicable regulatory framework for such products as well as any potential measures that may be done to enhance the effectiveness and efficiency of the regulatory process for a particular product (63). Early communication with the FDA and its centers is essential to efficiently plan and advance along the regulatory pathway, even though future opportunities to support and clarify this regulatory process must be encouraged (61).

b) Ethical Challenges for Targeted Implantable Delivery Systems

There are several implantable medical devices available today. It has been thought that the type of implants that connect with body tissues has particularly serious ethical consequences (64). Some of these ethical concerns are being addressed by the "EPIONE" project, which is financed by the EU. The initiative is attempting to enhance the safety and efficiency of these devices while also providing recommendations for the moral use of implantable medication delivery systems. This review discussed some of them (64, 65);

Privacy: The information gathered by implantable medication delivery systems may be used to track patients without their permission or to exclude them from insurance coverage or the workforce. For instance, an insurance provider or an employer may utilize information from a patient's implantable drug delivery system to refuse them coverage or a job.

Informed consent: Patients who receive implantable medication delivery systems might not be completely aware of the dangers and negative effects of the medical technology. They might not be aware that they can be removed, turned off, or eventually need to be replaced. Patients may choose treatments that are not in their best interests as a result of this lack of informed consent.

Cost: Patients may not be able to purchase implantable drug delivery systems because of their high cost. Patients may be required to pay for these gadgets out of pocket if insurance companies do not cover their costs. The high price of implantable drug delivery devices may make it impossible for some patients to receive the necessary care.

Safety: Because implantable medication delivery systems are still being developed, there is a chance that they could break down or become infected. Patients have occasionally lost their lives as a result of complications with these devices. Implantable drug delivery devices' potential for damage may deter patients from receiving the necessary care.

c) Future opportunities for epidural and intrathecal delivery systems

Compared to conventional methods of administration, medication implant technology can deliver drugs more precisely, locally, and for longer periods, with fewer adverse effects (66). For more than 30 years, epidural and intrathecal drug delivery devices (EIDDS) have been utilized to treat chronic pain. Compared to conventional pain relief techniques like oral pills and injections, these systems have several benefits, including improved accuracy and efficiency of medication delivery, less chance of adverse effects, and improved patient compliance (12). Future applications for EIDDS technology in chronic pain management are numerous as the technology develops. These consist of (13, 67-69):

Use of new drugs and drug combinations; Numerous medications, such as opioids, local anesthetics, and anticonvulsants, can be administered with EIDDS. when new drugs are developed for chronic pain, EIDDS can be the best way to deliver these drugs in a more effective and targeted way.

The use of personalized medicine; According to the requirements of each patient, EIDDS can be utilized to provide medications in a tailored manner. This can entail using genetic testing to pinpoint individuals who are more likely to respond to particular medications or using real-time monitoring to modify drug administration based on the patient's level of discomfort.

The development of wireless EIDDS; Current EIDDS systems demand that patients refill their drug reservoirs at a doctor's office. Wireless EIDDS would enable patients to top out their reservoirs at home, increasing convenience and lowering treatment costs.

A bright future is provided by EIDDS for the treatment of chronic pain. EIDDS are probably going to get cheaper, more practical, and more efficient as technology develops (13).

The potential for developing targeted implantable medication delivery systems to treat chronic pain is enormous. These systems are designed to deliver drugs in a sustained and controlled manner, avoiding systemic administration and minimizing any potential negative effects. Nanotechnology and materials science developments have made it possible to create implanted devices with precise and regulated medication delivery capabilities. For the best pain treatment for specific individuals, these devices can be configured to deliver medication at specified times and in specific amounts (70, 71).

The creation and broad application of targeted implantable medication delivery devices for chronic pain, however, face several obstacles. These comprise assuring the implant's long-term stability and biocompatibility, creating trustworthy techniques for observing and modifying medication release, and resolving potential problems such as device migration or infection. Despite these difficulties, efforts are being made to advance the field of tailored implanted medication delivery devices for chronic pain through ongoing research and development. These technologies have the potential to transform pain management and improve the quality of life for those with chronic pain with additional invention and improvement (72).

Conclusion

Using epidural and intrathecal drug delivery devices (EIDDS) to alleviate chronic pain is a promising strategy. These systems make it possible to deliver medication right to the location of the pain, which might assist in lowering the dosage needed and lessen adverse effects. Additionally, EIDDS can be set up to dispense medication according to a specified schedule, helping to guarantee that patients get the proper medication at the right time. Numerous high-quality randomized controlled trials and economic analyses have been used to assess its efficacy, safety, and cost-effectiveness. All forms of pain, including those that are still challenging to treat with traditional methods, can now be targeted with devices and treatments. EIDDS significantly lowers the hazards related to systemic therapies, such as opioids, for refractory cancer pain. With implantations performed by specialized facilities, refills administered by compounding pharmacies, and follow-ups handled by advanced nurse practitioners closer to patients' homes, the limited access to EIDDS therapy may be improved. Research activities and novel techniques are currently being conducted in the field of implantable drug delivery systems. Researchers are still optimistic that many of these systems will eventually be created with optimal zero-order release kinetics profiles that would work well in vivo for lengthy periods and allow for prolonged use in a patient with chronic pain. EIDDS is a promising new treatment option for chronic pain treatment.

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Reference

1. Laura Smith. Chronic Pain Statistics: US & Global Prevalence: The good body; 2022 [Available from: https://www.thegoodbody.com/.
2. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The link between depression and chronic pain: neural mechanisms in the brain. Neural plasticity. 2017;2017.

3. Petrosky E, Harpaz R, Fowler KA, Bohm MK, Helmick CG, Yuan K, et al. Chronic pain among suicide decedents, 2003 to 2014: findings from the national violent death reporting system. Annals of internal medicine. 2018;169(7):448-55.
4. Specialists SP. STOP THE CYCLE OF CHRONIC PAIN & SLEEPLESS NIGHTS 2019 [Available from: https://www.southsidepainspecialists.com/stop-the-cycle-of-chronic-pain-sleepless-nights/.
5. Hadi MA, McHugh GA, Closs SJ. Impact of chronic pain on patients' quality of life: a comparative mixed-methods study. Journal of patient experience. 2019;6(2):133-41.
6. Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, et al. The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice. Pharmaceutics. 2023;15(4):1165.
7. Andresen T, Niesters M, Dahan A, Morlion B, Drewes AM. Pharmacological management of chronic pain: how to deal with the catch-22 situation. Journal of Current Medical Research and Opinion. 2021;4(2):773-92.
8. James R, Toti US, Kumbar SG, Laurencin CT. Diseases and clinical applications that can benefit from long lasting implants and injections. Long Acting Injections and Implants. 2012:93-111.
9. Weld ED, Flexner C. Long-acting implants to treat and prevent HIV infection. Current Opinion in HIV and AIDS. 2020;15(1):33.
10. Jain KK. Drug delivery systems-an overview. Drug delivery systems. 2008:1-50.
11. Picco CJ, Domínguez-Robles J, Utomo E, Paredes AJ, Volpe-Zanutto F, Malinova D, et al. 3D-printed implantable devices with biodegradable rate-controlling membrane for sustained delivery of hydrophobic drugs. Drug Delivery. 2022;29(1):1038-48.
12. Pons-Faudoa FP, Ballerini A, Sakamoto J, Grattoni A. Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases. Biomedical microdevices. 2019;21:1-22.
13. Gao J, Karp JM, Langer R, Joshi N. The future of drug delivery. ACS Publications; 2023. p. 359-63.
14. Billings C, Anderson DE. Role of implantable drug delivery devices with dual platform capabilities in the prevention and treatment of bacterial osteomyelitis. Bioengineering. 2022;9(2):65.
15. Lister S, Hofland J, Grafton H, Wilson C. The Royal Marsden manual of clinical nursing procedures: John Wiley & Sons; 2021.
16. Farquhar-Smith P, Chapman S. Neuraxial (epidural and intrathecal) opioids for intractable pain. British Journal of Pain. 2012;6(1):25-35.
17. Macintyre PE, Schug S, Scott D, Visser EJ, Walker SM. Acute pain management: scientific evidence: Australian and New Zealand College of Anaesthetists; 2010.
18. Brorsen A, Rogelet K. BOOK ALONE-CEN Examination Review: Jones & Bartlett Publishers; 2011.
19. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). pain. 2019;160(1):19-27.
20. Rauck RL, Cherry D, Boyer MF, Kosek P, Dunn J, Alo K. Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain. The Journal of Pain. 2003;4(8):441-7.
21. Smith T, Coyne P, Staats PS, Deer T, Stearns L, Rauck R, et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). Annals of Oncology. 2005;16(5):825-33.
22. Gerber HR. Intrathecal morphine for chronic benign pain. Best Practice & Research Clinical Anaesthesiology. 2003;17(3):429-42.
23. Hunter CW, Lee ET, Masone R, Deer TR. Disease indications. Atlas of Implantable Therapies for Pain Management. 2016:11-4.
24. De Andres J, Asensio-Samper JM, Fabregat-Cid G. Advances in intrathecal drug delivery. Current Opinion in Anesthesiology. 2013;26(5):594-9.
25. Czernicki M, Sinovich G, Mihaylov I, Nejad B, Kunnumpurath S, Kodumudi G, et al. Intrathecal drug delivery for chronic pain management-scope, limitations and future. Journal of Clinical Monitoring and Computing. 2015;29:241-9.
26. Khazaei Z, Sohrabivafa M, Momenabadi V, Moayed L, Goodarzi E. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide prostate cancers and their relationship with the human development index. Advances in Human Biology. 2019;9(3):245.
27. He Q-H, Liu Q-L, Li Z, Li K-Z, Xie Y-G. Impact of epidural analgesia on quality of life and pain in advanced cancer patients. Pain Management Nursing. 2015;16(3):307-13.
28. Sindt JE, Odell DW, Dalley AP, Brogan SE. Initiation of intrathecal drug delivery dramatically reduces systemic opioid use in patients with advanced cancer. Neuromodulation: Technology at the Neural Interface. 2020;23(7):978-83.
29. Abdelemam RM, Fares KM, Kamal SM. Effect of Combined Epidural Morphine and Midazolam on Postoperative Pain in Patients Undergoing Major Abdominal Cancer Surgery. The Clinical Journal of Pain. 2022;38(11):693-9.
30. Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, et al. Intrathecal drug delivery systems for cancer pain: an analysis of a prospective, multicenter product surveillance registry. Anesthesia and Analgesia. 2020;130(2):289.
31. Sayed D, Monroe F, Orr WN, Phadnis M, Khan TW, Braun E, et al. Retrospective analysis of intrathecal drug delivery: outcomes, efficacy, and risk for cancer-related pain at a high volume academic medical center. Neuromodulation: Technology at the Neural Interface. 2018;21(7):660-4.
32. Bolash R, Udeh B, Saweris Y, Guirguis M, Dalton JE, Makarova N, et al. Longevity and cost of implantable intrathecal drug delivery systems for chronic pain management: a retrospective analysis of 365 patients. Neuromodulation: Technology at the Neural Interface. 2015;18(2):150-6.
33. Eldabe S, Duarte RV, Madzinga G, Batterham AM, Brookes ME, Gulve AP, et al. Comparison of the effects of intermittent boluses to simple continuous infusion on patients' global perceived effect in intrathecal therapy for pain: a randomized double-blind crossover study. Pain Medicine. 2017;18(5):924-31.
34. Hamza M, Doleys DM, Saleh IA, Medvedovsky A, Verdolin MH, Hamza M. A prospective, randomized, single-blinded, head-to-head long-term outcome study, comparing intrathecal (IT) boluses with continuous infusion trialing techniques prior to implantation of drug delivery systems (DDS) for the treatment of severe intractable chronic non-malignant pain. Neuromodulation: Technology at the Neural Interface. 2015;18(7):636-49.

35. Hayes C, Jordan MS, Hodson FJ, Ritchard L. Ceasing intrathecal therapy in chronic non-cancer pain: an invitation to shift from biomedical focus to active management. PLoS One. 2012;7(11):e49124.
36. Yoo Y, Oh JH, Lee H, Choi H, Joo S, Han AH, et al. Myth and Truth in Opioid Consumption with Intrathecal Morphine Pump Implantation in Chronic Pain: A Retrospective Cohort Study with Claims Database in South Korea. Pain Medicine. 2023;24(1):79-88.
37. Stark CW, Isaamullah M, Hassan SS, Dyara O, Abd-Elsayed A. A Review of Chronic Pain and Device Interventions: Benefits and Future Directions. Pain and Therapy. 2023;12(2):341-54.
38. Desjardins P, Ménassa M, Desbiens F, Gagné J-P, Hogue J-C, Poirier É. Effect of single-shot intrathecal morphine versus continuous epidural analgesia on length of stay after gastrectomy for cancer: a retrospective cohort study. Gastric Cancer. 2023:1-5.
39. Collins J, Dixon M, Peng J. Optimal Pain Management after Open Whipple: Comparison of Epidural versus Intrathecal (IT) Morphine Plus Transversus Abdominis Plane Block versus TAP Block Alone. HPB. 2022;24:S404-S5.
40. Deer TR, Pope JE, Hayek SM, Lamer TJ, Veizi IE, Erdek M, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for intrathecal drug delivery: guidance for improving safety and mitigating risks. Neuromodulation: Technology at the Neural Interface. 2017;20(2):155-76.
41. Rauck RL, Wallace MS, Leong MS, MineHart M, Webster LR, Charapata SG, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. Journal of pain and symptom management. 2006;31(5):393-406.
42. Alicino I, Giglio M, Manca F, Bruno F, Puntillo F. Intrathecal combination of ziconotide and morphine for refractory cancer pain: a rapidly acting and effective choice. Pain. 2012;153(1):245-9.
43. Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S, et al. The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation: Technology at the Neural Interface. 2017;20(2):96-132.
44. Fayaz A, Croft P, Langford R, Donaldson L, Jones G. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ open. 2016;6(6):e010364.
45. Brogan SE, Winter NB, Abiodun A, Safarpour R. A cost utilization analysis of intrathecal therapy for refractory cancer pain: identifying factors associated with cost benefit. Pain Medicine. 2013;14(4):478-86.
46. Stearns LJ, Narang S, Albright RE, Hammond K, Xia Y, Richter HB, et al. Assessment of health care utilization and cost of targeted drug delivery and conventional medical management vs conventional medical management alone for patients with cancer-related pain. JAMA Network Open. 2019;2(4):e191549-e.
47. Capozza MA, Triarico S, Mastrangelo S, Attinà G, Maurizi P, Ruggiero A. Narrative review of intrathecal drug delivery (IDD): indications, devices and potential complications. Annals of Translational Medicine. 2021;9(2).
48. Hustak EC, Engle MP, Viswanathan A, Koyyalagunta D. Lumbar subarachnoid hematoma following an epidural blood patch for meningeal puncture headache related to the implantation of an intrathecal drug delivery system. Pain physician. 2014;17(3):E405.
49. Brand FM, Mchaourabiano AS, Veneziano G. Implantable intrathecal pumps for chronic pain: highlights and updates. Croatian medical journal. 2007;48(1):22-34.
50. De Andrés J, Rubio-Haro R, De Andres-Serrano C, Asensio-Samper JM, Fabregat-Cid G. Intrathecal drug delivery. Drug Delivery Systems. 2020:75-108.
51. Krames E. Implantable devices for pain control: spinal cord stimulation and intrathecal therapies. Best Practice & Research Clinical Anaesthesiology. 2002;16(4):619-49.
52. Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. Pain physician. 2011;14(3):219.
53. Deer TR, Hayek SM, Pope JE, Lamer TJ, Hamza M, Grider JS, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for trialing of intrathecal drug delivery infusion therapy. Neuromodulation: Technology at the Neural Interface. 2017;20(2):133-54.
54. Teng W-N, Tsou M-Y, Chang W-K, Ting C-K. Eyes on the needle: Identification and confirmation of the epidural space. Asian journal of anesthesiology. 2017;55(2):30-4.
55. Brogly N, Guasch E, Alsina E, García C, Puertas L, Dominguez A, et al. Epidural Space Identification With Loss of Resistance Technique for Epidural Analgesia During Labor: A Randomized Controlled Study Using Air or Saline—New Arguments for an Old Controversy. Anesthesia & Analgesia. 2018;126(2):532-6.
56. Sng BL, Sia ATH. Maintenance of epidural labour analgesia: The old, the new and the future. Best Practice & Research Clinical Anaesthesiology. 2017;31(1):15-22.
57. Abd-Elsayed A, Karri J, Ashley M, Bryce D, Sun J, Maxwell L, et al. Intrathecal drug delivery for chronic pain syndromes: a review of considerations in practice management. Pain Physician. 2020;23(6):E591.
58. Schultz DM, Orhurhu V, Khan F, Hagedorn JM, Abd-Elsayed A. Patient satisfaction following intrathecal targeted drug delivery for benign chronic pain: results of a single-center survey study. Neuromodulation: Technology at the Neural Interface. 2020;23(7):1009-17.
59. Reck T, Chang E-C, Béchir M, Kallenbach U. Applying a part of the daily dose as boli may improve intrathecal opioid therapy in patients with chronic pain. Neuromodulation: Technology at the Neural Interface. 2016;19(5):533-40.
60. Hawley P, Beddard-Huber E, Grose C, McDonald W, Lobb D, Malysh L. Intrathecal infusions for intractable cancer pain: a qualitative study of the impact on a case series of patients and caregivers. Pain Research and Management. 2009;14:371-9.
61. Al-Jawadi S, Capasso P, Sharma M. The road to market implantable drug delivery systems: a review on US FDA's regulatory framework and quality control requirements. Pharmaceutical Development and Technology. 2018;23(10):953-63.
62. Liang C-P, Sack C, McGrath S, Cao Y, Thompson CJ, Robin LP. US Food and Drug Administration regulatory pesticide residue monitoring of human foods: 2009-2017. Food Additives & Contaminants: Part A. 2021;38(9):1520-38.

63. Rock CM, Brassill N, Dery JL, Carr D, McLain JE, Bright KR, et al. Review of water quality criteria for water reuse and risk-based implications for irrigated produce under the FDA Food Safety Modernization Act, produce safety rule. Environmental research. 2019;172:616-29.
64. Telléus PK, Jensen W. Ethical Assessment and Reflection in Research and Development of Non-Conformité Européene Marked Medical Devices. Cambridge Quarterly of Healthcare Ethics. 2020;29(4):592-606.
65. Juengst E, Siegel R. Subtracting injury from insult: ethical issues in the use of pharmaceutical implants. Hastings Center Report. 1988;18(6):41-6.
66. Stuart A. The promise of implantable drug delivery systems. American Academy of 1042 Ophthalmology. 2010.
67. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomaterials Research. 2020;24(1):1-12.
68. Laracuente M-L, Marina HY, McHugh KJ. Zero-order drug delivery: State of the art and future prospects. Journal of Controlled Release. 2020;327:834-56.
69. Kumar A, Pillai J. Implantable drug delivery systems: An overview. Nanostructures for the engineering of cells, tissues and organs. 2018:473-511.
70. Salave S, Rana D, Sharma A, Bharathi K, Gupta R, Khode S, et al. Polysaccharide based implantable drug delivery: Development strategies, regulatory requirements, and future perspectives. Polysaccharides. 2022;3(3):625-54.
71. Wang J, Zhang Y, Aghda NH, Pillai AR, Thakkar R, Nokhodchi A, et al. Emerging 3D printing technologies for drug delivery devices: Current status and future perspective. Advanced Drug Delivery Reviews. 2021;174:294-316.
72. Rafiei F, Tabesh H, Farzad F. Sustained subconjunctival drug delivery systems: Current trends and future perspectives. International Ophthalmology. 2020;40:2385-401.