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Device use in chronic pain

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ABSTRACT

Interventional treatments are of vital importance in patients with chronic pain who do not respond to conventional drug therapy. Neuraxial drug delivery systems can be used for intractable cancer-induced pain. These devices, which are frequently used today and have advanced technological equipment, provide effective analgesia to patients. Another technique preferred especially in neuropathic pain is implantable devices that provide neurostimulation. Spinal cord stimulation (SCC) and Dorsal root ganglion stimulation (DRG-S) are the most commonly used. This article describes frequently used devices that provide neurostimulation and neuroaxial drug delivery device are mentioned, and their working principles, application techniques, and technological features. Pubmed and Google scholar were used to search the articles, and Google was used for device images and manufacturer information.

Keywords: Neuraxial infusion, neurostimulation methods, chronic pain, neuropathic pain.

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Introduction

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience related to real or potential tissue damage [1]. Pain is a complex condition that is affected by psychosocial and iatrogenic factors, along with a series of changes in the nervous system [2].

The time taken for the pain to be defined as chronic is known as 3-6 months [3]. While chronic somatic pain affects 20% of the general population; the rate of neuropathic pain is 9% [4]. WHO treatment algorithm can be used in the treatment of chronic pain. There is a large group of drugs included in the algorithm with oral use. The drugs included in this algorithm are sufficient for most patients with chronic pain [5]. Interventional treatments can be applied in the treatment of chronic pain who cannot take oral medication, cannot tolerate drug side effects, or do not respond to such treatment. Interventional treatments comprise drug delivery systems and stimulators [6,7]. Such treatments are applications that require experience [8].

This article focuses on intrathecal drug delivery devices, spinal cord stimulators, and dorsal root ganglion stimulators.

In this review, we performed a Pub Med search with the following search words: perineural infusion, neuraxial infusion for chronic pain, intrathecal infusion device, epidural infusion for chronic pain, perineural infusion, neurostimulation methods for chronic pain, mechanisms of dorsal root ganglion stimulation, DRG stimulation for chronic pain, dorsal root ganglion stimulation to treat

complex regional pain syndrome, spinal cord stimulation for chronic pain, and mechanisms of spinal cord stimulation. In addition, in our Google and Google scholar search, we used the keywords: Algomed infusion system, SynchroMed Infusion system, and for this purpose, we examined clinical studies and reviews up to 2022.

Drug delivery systems: Perineural and neuraxial (epidural, intrathecal) infusions have been used for many years in patients with chronic pain. These interventional procedures can be called minimally invasive interventions [9]. It is based on the principle of delivering drugs to the targeted area with the help of a catheter.

The rate of patients admitted to pain clinics because of cancer-related pain is significantly higher [9]. Opioid analgesics form the basis of pharmacological treatment in these patients. In routine use, oral forms of weak and moderately effective opioids are preferred in the first two steps. In the advanced step (third step), fentanyl with transdermal form is preferred. Recent studies show that cancer pain is inadequately treated. The 5-year survival rate for all cancers is 65% [10] and most of the surviving patients experience chronic pain [11] Res-Pina P et al. [12] reported the under treatment rate as 25.6%, while Singh H [13] reported this rate as 77%.

Using neuraxial drug infusion devices may be considered in patients with persistent pain who cannot respond to conventional medical treatment [14]. In pain caused by cancer, intrathecal infusion systems have some advantages such as better pain management; high patient satisfaction, rapid onset of action, and fewer cancer-related symptoms [15]. They also have some disadvantages such as high cost and infection [14]. There are some prerequisites for the use of these devices. The patient does not have sufficient intellectual capacity to use the device, a communication network that the patient can reach when needed, and expert personnel, home care services infrastructure for cases that require observation such as drug overdose and side effects [16]. Intrathecal drug delivery pumps were first used in 1981. These pumps can also be used for non-cancer, chronic pain [17,18]. In patients with chronic pain, drugs can be given to the subarachnoid area and effective analgesia can be provided by administering medication to the epidural area. Epidural infusion has been used for many years in both persistent cancer pain [19] and chronic pain, such as post-herpetic neuralgia and Foot drop syndrome, apart from malignancy [20]. Neuraxial Drug Delivery Systems vary in technology depending on the parts that can be implanted.

While those that can only be implanted with the catheter have simpler technology, there are devices equipped with advanced technology, with an external control panel, where the reservoir and pump can also be implanted**.** Drug delivery systems where only the catheter is implanted: the catheter is placed percutaneously; the reservoir and the pump are outside Figure 1. These catheters are designed for short-term use. It can be preferred in patients with a short life expectancy and in whom pain palliation cannot be achieved despite traditional treatment. The catheter can be tunneled under the skin to prolong the service life of percutaneously placed catheters. Thus, the dislodgement of the catheter can be prevented. Drug delivery devices comprise three components: catheter, reservoir, and pump. The pump has manual or programmable variants. While manual pumps provide a fixed dose of medication, programmable pumps also have a button system for sending bolus doses. Programmable pumps have three different modes: continuous infusion, continuous

Figure1. Patient-controlled analgesia devices.
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infusion + intermittent bolus, or intermittent bolus. The continuous infusion mode is the continuous delivery of a fixed dose of medication with the aid of the device. If a bolus mode is chosen, the dose and time must be adjusted to prevent overdose. Boluses are administered by the patient with the help of a button connected to the device. These devices are called patient-controlled analgesia (PCA) devices. Apart from these devices, elastomeric pumps can do the same work with patients with chronic pain. These pumps are used in manual forms, but there are also forms with programmable features [21]. While providing a continuous drug concentration in the target area with the help of PCA devices, the patient can administer a bolus dose of medication during pain attacks. Thus, the patient becomes a part of the treatment [21].

Drug delivery systems where a catheter, reservoir, and pump can also be implanted: This group includes the "Algomed" drug delivery device with a manual pump designed for intrathecal drug use, and the "SynchroMed" drug delivery device with a sophisticated external programmable pump. The Algomed drug delivery device is a patient-controlled analgesia system used to provide morphine infusion, especially in cancer patients. This system delivers 1 mL bolus dose of morphine each time it is activated. The patient must wait for the 60-90 min refill time to activate the second bolus dose. In this way, overloading is prevented. The need for dosage increase is met by increasing the drug concentration [22]. The Synchromed™ II intrathecal pump is one of the most advanced technology among modern intrathecal drug delivery devices used in the treatment of chronic pain. The system comprises two hardware and three pieces of software. The first part of the hardware is called the “SynchroMed™ II Pump” and it houses the drug reservoir, electronic control unit, two inlet ports, and a battery (Figure 2).

Figure 2. SynchroMed™ II Pump. (Copyright Notice: https://www.medtronic.com/us-en/healthcare-professionals/therapies-procedures/neurological/targeted-drug-delivery/reimbursement-practice-management/media-kit.html)

Two different types of pumps have been introduced to the market, with a reservoir capacity of 20 ml and 40 ml. The pump unit has a life of 7 years with a daily flow of 0.9 ml, the margin of error is ± 0.3%, it is compatible with magnetic resonance procedures (1.5-3 tesla), it can stop working in MR examinations and continue its function after the procedure, its reservoir for MR no need to be emptied. The second hardware unit, known by the trade name "Ascenda™ Catheter", was launched in two different lengths, 114 cm and 140 cm, resistant to crushing, 1.2 mm outer 0.5 mm inner diameter, 6 holes lined up at the end [23,24]. There are three different types of software available and are named "Synchromed™ II Clinician Programmer", "MyPTM™", and "Efficio™ Management Software" [25]. While using Synchromed™ II Clinician Programmer, the physician can determine the working system of the device and the appropriate free dose ranges for the patient. With MyPTM, patients can set their own dose modifications within the limits defined by the clinician. This program needs a transmitter named My PTM™ and a communicator to run [26]. With Efficio™ Management Software, the device's operating history, schemas of past doses, and optional device access are managed [27]. Synchromed II is commercially named "The Control Workflow™," have a system that provides targeted drug delivery. The device allows the intrathecal administration of preservative-free morphine hydrochloride and preservative-free ziconotide in patients with malignant chronic pain. The device has two input ports. Medication can be loaded from the reservoir port. The catheter port can also be used in cases where acute drug administration is required. The working principle of the reservoir section is to compress a pressurized gas adjusted to body temperature while the drug is loaded from the reservoir port by injection, and transmit the pressure, thus generated to the catheter with a peristaltic movement with valve systems as a propulsive mechanism. The catheter is often placed in the lumbar region and can be raised to the desired level. The main unit is implanted under the skin on the abdominal sidewall in the subcostal region by tunneling. Although the accuracy and reliability of the device are proven in some clinical studies [28], complications related to device failure have been reported in some studies [29,30]. Another infusion site is the peripheral nerves. Perineural infusion is known as the delivery of local anesthesia to a peripheral nerve with the help of a percutaneous catheter. It was first described by Ansbro FP in 1946 [31]. Introducing ultrasound in clinical practice has made this interventional procedure

more reliable. The target peripheral nerve is identified by ultrasound and the catheter can be safely advanced near the nerve. It is used for postoperative pain. It can also be preferred in patients with chronic pain, such as complex regional pain syndrome [32**],** trigeminal neuralgia [33], and cancer-induced pain [34]. The pumps can also be used in this area. While complications can be observed depending on the location of the catheter (such as infection due to the femoral catheter, pneumothorax due to the interscale catheter), nerve damage and pain during the procedure are common complications.

Neurostimulation devices:

Using electrical stimulation in neurophysiological research dates back to the second half of the nineteenth century (1850–1920). Since these dates, new electrode designs, clinical practice experience and treatment protocols have been developed with technological progress and have reached the present day. A neurostimulator device in its simplest form comprises a power source (battery), a pair of electrodes, and a connecting cable that connects the electrode to the battery. There are two different types of electrodes are used for stimulation, monopolar and bipolar. When using a bipolar electrode, both the negative and positive electrodes are in the target tissue. In the monopolar electrode, the negative electrode is inside the target tissue, but the positive electrode having a large surface is far from the target tissue. Neurostimulation techniques can be divided into invasive and noninvasive. Examples of non-invasive stimulation techniques are transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation, repetitive transcranial magnetic stimulation, Remote electrical neuromodulation. Invasive stimulation techniques also consist of occipital nerve stimulation, vagus nerve stimulation, spinal cord stimulation, deep brain stimulation, dorsal root ganglion stimulation, and peripheral nerve stimulation.

Spinal cord stimulation: Shealy et al first described Neurostimulation of the spinal cord in 1967. In intractable cancer pain [35] and its mechanism of action is explained by the door control theory put forward by Melzack and Wall. According to this theory, the spinal cord acts as a gate to the Substantia gelatinosa in the dorsal horn and is controlled by large diameter Aβ fibers and small diameter of Aδ and C fibers. It was hypothesized that stimulation of large diameter Aβ fibers would inhibit nociceptive signals transmitted by small Aβ and C fibers (closure of the pain-related gate) [36,37]. Stimulation of Aβ fibers by SCS increases the activation of inhibitory interneurons and inhibits wide dynamic range (WDR) neurons, thus reducing the increased pain signal [38,39]. Conventional SCS stimulates large Aβ fibers by generating mild electrical pulses at a frequency, intensity of 30-60 Hz. The resulting paresthesia overlaps with the patient's painful area, creating pain relief [40,41]. The SCS effect mechanism cannot be limited to the door control theory. Because acute pain in the area of paresthesia created by SCS cannot be prevented. SCS also treats the symptom of allodynia of neuropathic pain. Another reason suggesting the existence of different mechanisms of action is that the same rate and complete pain relief cannot be achieved in every patient. Possible mechanisms of action are explained outside the gate control theory of SCS; as a neurochemical effect, SCS regulates the balance between inhibitory and excitatory effects in the dorsal horn and restores decreased GABA levels. In addition, it has been

shown that it can reduce neuropathic pain by providing pain modulation through GABAergic, serotonergic, adrenergic, cholinergic, and adenosine-dependent mechanisms [41,42]. SCS restores the oxygen demand-delivery balance in the tissues, reducing the sympathetic tone. It also shows anti-anginal and anti-ischemic effects with sympathetic nervous system modulation. It has been reported that the anti-ischemic effect is because of the release of vasoactive substances [43] and the anti-anginal effect is because of the stabilization of intra-cardiac neuronal activity [44]. Spinal cord stimulators comprise four components. (Figure 3).

1. A neurostimulator that produces an electric pulse,
2. Electrodes placed in the epidural space
3. Extension wires that connect the electrodes to the neurostimulator
4. Remote control that programs the neurostimulator [45].

The neurostimulator has two different technologies an implantable pulse generator having a battery and devices that produce external radiofrequency pulses. The implantable pulse generator is also divided into two according to whether or not it is recharged and is usually tunneled into the space above the hip. There are two different types of electrodes, percutaneous and surgical. When surgical electrodes and percutaneous electrodes are compared, surgical electrodes require laminectomy when placed in the epidural space, which is a disadvantage, while less risk of migration is an advantage. Surgical electrode paddle-type was manufactured, whereas the percutaneous electrode was produced cylindrical to pass through the Tuohy needle. The cylindrical structure of percutaneous electrodes reduces battery life by increasing energy consumption [46]. Battery duration may vary according to usage-related parameters such as pulse, voltage, frequency, etc., [47].

Figure 3. Spinal cord stimulators components.
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The battery life of recently produced rechargeable batteries has been reported as 10-25 years [48]. Critical stimulation parameters for SCS are stimulation frequency, stimulation amplitude, waveform pulse width, and electrode geometry. Recently, new stimulation modalities such as burst stimulation, high frequency (> 1000 Hertz) stimulation have been added to the conventional SCS. The FDA in certain diseases that cause chronic neuropathic pain in the trunk and extremities has approved electrical stimulation of the spinal cord. Failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) are the two most common indications for which SCS is used. SCS applied to 254 patients with neuropathic pain after lumbar surgery. It was reported that pain relief was good to excellent in 68% of the patients in their 4-year follow-up [50]. In another observational study, SCS was performed on 182 patients with neuropathic pain after laminectomy. At approximately 8-year follow-up, 48% of patients experienced 50% or greater long-term pain relief with SCS [51]. In a review of FBSS patients, nine observational studies were examined. It has been observed that the long-term pain (> one-year) relief rate with SCS varies between 48-71% [52]. The second most common indication for SCS is CPRS. In a case series of 8 patients with neuropathic pain because of CRPS in the upper extremity, a temporary percutaneous catheter was applied at the C5-7 level. A permanent catheter was implanted after a 10-day trial period. At 27-month follow-up, 87.5% of patients described pain relief as good to excellent [53]. In a randomized controlled study on 54 patients with chronic reflex sympathetic dystrophy, the Spinal cord stimulation (SCS) test + physical therapy was applied to 36 patients, and only physical therapy was applied to 18 patients. SCS trial stimulation failed in 12 of the patients in the SCS+PT group, and SCS implantation was performed in 24 patients. In the 1-year follow-up of the patients, it was observed that VAS scores decreased significantly in the SCS+ PT group, while VAS values increased in the PT group. Other indications for using SCS are refractory angina pectoris[54], peripheral vascular disease[55], phantom limb pain[56], intractable postherpetic neuralgia[57], persistent post-thoracotomy pain[58], chronic head and facial pain[59], and can be listed as refractory abdominal visceral pain[60]. Because of the entry into the epidural space, coagulopathy, use of anticoagulants, and the presence of infection at the site of the intervention are contraindications. In addition, this procedure should not be applied to patients with a short life expectancy. Complications of SCS It can be observed in the intraoperative or postoperative (early-late period) period. When these complications are listed according to the frequency of occurrence, the most common lead migration is seen. Other complications can be listed as follows in decreasing frequency: lead breakage, infection, hardware malfunction, unwanted stimulation, battery failure, loose connection, epidural hematoma, cerebrospinal fluid leakage, pain over the implant, skin erosion, allergic reaction, paralysis [61].

Dorsal root ganglion stimulation: DRG is anatomically composed of Soma, axon, and dendrite. DRG contains sensory nerve cell groups that provide transmission and modulation of pain [62]. Due to this structural feature, chronic pain treatment has also been the focus of attention.
For the treatment of chronic pain, surgical operations such as dorsal rhizotomy or ganglionectomy can be applied to this region. In addition, minimally invasive interventions

such as local anesthetic infiltrations, steroid infiltration, conventional and pulsed radiofrequency denervation, DRG stimulation can also be applied [63]. Although the mechanism of action of DRG-S used in the treatment of chronic pain is not clearly known, four hypotheses have been put forward. The first is "modulation of the sympathetic pathways and neural activity." The second theory is the "change in ion channel expression and decrease in inflammatory markers in DRG somata." The third theory is that "DRG acts as a filter for afferent PSN activity. Calcium current changes caused by injury disrupt the filtering feature of DRG and allow high-frequency currents to pass through. DRGS can bring the deteriorated filtering threshold back to normal levels" [42]. Fourth theory is that "stimulation at very low frequencies (0.5–5 Hz) is claimed to activate the natural endogenous opioid system." It is known that low-frequency signals (<20 Hz) have an inhibitory effect in the dorsal horn, while high-frequency signals (>25 Hz) have a stimulatory effect [64]. DRG-S acts by generating an electric field at or near the soma of DRG. The level of intervention is determined by the PSN, which innervates the painful body dermatome of the patient. The set of DRG-S consists of three components Implantable power generator (IPG) that have the option of up to four leads and 32 contacts. IPG is non-rechargeable and provides constant current stimulation. The IPG can be placed by creating a pocket under the skin in the upper hip or abdomen. The leads transmit electrical pulses from the power generator to the target DRG. Leads are thin wires with a flexible, insulated structure.

The procedure is based on placing a lead at or near the DRG. The interventional procedure is performed under sedation and guided by fluoroscopy. The epidural space can be accessed by the trans-foraminal or interlaminar route and a Touhy needle is used. After interlaminar epidural access, the DRG can be reached via a contralateral route. The lead containing stylet is loaded into a delivery sheath and delivered to the epidural space via the Tuohy needle. It is advanced along the foramen under fluoroscopy and is ensured that the sheath reaches the DRG same or near the same. Lead placement is confirmed by ensuring that the paresthesia induced by stimulation overlaps with the patient's painful area, and this is achieved by patient feedback. After that, the sheath and needle are removed. The leads are provided to reach the IPG pocket by creating a tunnel under the skin. Before permanent implantation, approximately 1 week of trial stimulation is performed. Trial stimulation is done with an external stimulator and externalized led extension cables [42,63,65]. DRG S can be used in the treatment of Thoracic Neuralgia [66], Non-Complex Regional Pain Syndrome Related Chronic Pain Syndromes [67], complex regional pain syndrome [68], Diabetic Peripheral Neuropathy [69], Phantom Limb Pain [70], Chemotherapy-Induced Neuropathy [71], and failed back surgery syndrome [72]; but the success rate is different for each. Stelter B et al. [73], analyzed the data of 28 studies in which DRG S was performed for neuropathic pain. This systematic review consists of 158 patients. It has been reported that more than 50% of patients with low back pain have pain relief after DRG S. In the same way In patients with focal peripheral neuropathy (as Diabetic peripheral neuropathy, anterior cutaneous nerve entrapment syndrome, phantom limb pain, post-surgical, and post-infection peripheral neuropathies), pain relief after DRGS has been reported to be greater than 50% from baseline [73]. In another study, average low back pain relief was reported as

45.5% at 12 months [74]. As complications related to these interventions; reported lead migrations requiring surgery, and Pocket pain [75]. The Neuromodulation Appropriateness Consensus Committee has presented Consensus Recommendations regarding the use of DRGS in certain chronic pain syndromes. As parameters, They used the level of evidence (Level I, II-1, II-2, II-3, III) Grade of recommendation (Class A, B, C, D, I) Consensus (Strong, Moderate, and Low). They reported the use of DRGS in patients with focal neuropathic pain syndrome as Evidence level I, Grade A, Consensus Strong. This committee reported that while declaring CRPS type I or type II of the lower extremity as Level I, Grade a Strong Consensus, treatment for upper extremity CRPS type I or type II as Level II-2, Grade A, Consensus Strong. The effect of DRG stimulation in diabetic peripheral neuropathy (DPN) is based on limited data. (Level III, Grade C, and Consensus Strong).In non-diabetic peripheral neuropathy, case-by-case basis evaluation is recommended because the evidence is limited (Level III, Grade B, and Consensus Moderate). The NACC reported the use of DRGS in chronic postoperative surgery-induced chronic pain as Level III, Grade C, and Consensus Moderate. In the treatment of neuropathic groin pain, Level II-2 is suggested as Grade B, Strong Consensus. DRG stimulation in phantom limb pain is recommended for use in selected patients. Level III, Grade I, Consensus Moderate [74].

The main limitations of our review were that it was not a systematic review, and we did not mention deep brain stimulation and occipital nerve stimulation used in the treatment of headaches.

In Conclusion, this review provides a perspective on drug delivery systems used for the treatment of chronic pain treatment and the neuromodulatory devices SCS and DRGS, which are frequently used in especially neuropathic pain treatment. Drug delivery systems, spinal cord, and DRG stimulators working principles, application techniques, indications, contraindications, and complications were examined.

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