

Pain Management in Spinal Cord Injury: A Narrative Review

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Spinal cord injury (SCI) occurs due to any damage to the spinal cord and cauda equina. Most of the patients after spinal cord injury develop chronic pain, irrespective to the site and type of pain. This pain is severe in most of the cases and severely impairs the quality of life. The mechanisms responsible for the pain after spinal cord injury is poorly understood. The pain of SCI is basically classified in two main types: nociceptive or neuropathic. The objectives of this paper are to review the different treatment options for the SCI pain. The pain management after SCI includes pharmacological therapy and non-pharmacological therapy.

Keywords: Spinal cord injury; Pain mechanism; Pain management

Spinal cord injury (SCI) is a devastating problem that is characterized by loss of sensory, motor, and autonomic function as a result of partial or complete damage to the spinal cord and cauda equina [1-2]. However, the causes of spinal cord injury may be traumatic such as motor vehicle accidents, falls, and sports injuries or non-traumatic such as multiple sclerosis, tumors, and stenosis. The injuries of the spinal cord may be complete or incomplete, based on whether any movement and sensation occur at or below the level of injury. Different types of pain can occur after SCI, e.g. musculoskeletal pain, visceral pain and neuropathic pain. Musculoskeletal pain originated from bones, joints, ligaments and muscles either in the acute post-injury state or with chronic overuse. Whereas, visceral pain is caused by disturbances of bladder or bowel [3-4], neuropathic pain can occur as a result of lesion to the somatosensory system such as (spinal cord injury). In turn, neuropathic pain is also classified into at-level or below-level of neuropathic pain [3]. The reports recorded a scary number of SCI incidence in epidemiological studies in many countries. For instance, in the United States its prevalence is reported to be 12,000 new cases per year [5]. The incidence of spinal cord injury was in a high degree in men especially adults who are exposed to injuries related to sports, or accidents related to motor vehicle [1]. SCI is a serious medical condition that causes functional, psychological and socioeconomic disorders. Notoriously, medical complications due to SCI are serious such as respiratory, cardiovascular, urinary and

bowel complications, spasticity, pain syndromes, mechanical instability, pressure ulcers, osteoporosis and bone fractures [6]. In those patients who were exposed to spinal cord injury about half or third of them had pain, but the intensity was different among them. Chronic pain is the most common secondary complication in patients with spinal cord injury. Pain after SCI can occur in parts of the body where there is normal sensation as well as areas that have little or no feeling. The pain is real and can have a negative effect on different aspect of the life [6]. Intractable chronic pain remains a significant problem among complications for patients who complain of spinal cord injury. Recently, studies have been directed to estimate how those patients experience moderate to severe pain after SCI. Persistent pain for a long time will be associated with disturbance of the daily activities like sleep, and daily functions [7]. The prevalence of chronic pain in patients with SCI is about 65% and around one-third of them have severe pain. Some studies reported that up to 80 % of patients suffer chronic pain [8]. If pain continues for at least six months or longer, then is considered a chronic pain [9]. Since, in many cases chronic pain may be localized to the arms, trunk and legs, chronic pain and the abnormal sensation after SCI can interfere with functional impairment and independence [10].

Psychological aspects of pain are important in the experience and expression of pain and some authors suggested that the psychological factors considered as a type of pain that occurs after SCI. In addition to pain, the studies reported depression from the time of injury [11]. Most studies showed that continuous pain following SCI is associated with more depressive symptoms and greater perceived stress. In addition, there is a strong relationship among many conditions that accompanied SCI like pain, spasticity, abnormal nonpainful sensations, and sadness. Therefore, all methods of treatment should consider the psychological, social and environmental factors that may be contributing to the person's experience of pain [10,12]. Quality of life is lower in patients after SCI as compared with the normal population in all life aspects. But there is no difference in subgroups according to extent of lesion [13]. In addition, pain has a large impact on quality of life, may impair practice exercise for those patients with SCI. Pain may be a significant barrier to exercise adherence in

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individuals with SCI. Therefore, studies have been directed to assess the role of pain relief to promote exercise adherence in individuals with SCI and managing patients with SCI may increase the likelihood of exercise adherence in individuals with SCI. Although, exercise is more challenging in patients with SCI, it may alleviate many of the secondary health complications associated with SCI like psychological stress and promote a better quality of life [14]. However, in addition to the reductions in function and quality of life, the presence of pain negatively impacts inpatient rehabilitation therapy [15]. Therefore, patients with SCI are at risk of significant impairments in various aspects of their life. Pain after SCI is more difficult for the team who manages patients and also for the patients during rehabilitation. However, the suitable treatments require a precise assessment and identify the objectives of the treatment. Although, a complete pain relief is challenging and may be rare, but using interdisciplinary approaches and tremendous treatments are likely to minimize the pain to an acceptable level for those patients with SCI [5,9,15]. The practitioners of pain management try to teach some skills to those patients directly after SCI to reduce the negative effect of pain on their daily activities which may be beneficial [16]. By understanding, the pain mechanism and molecular, biochemical, and pathological events that generate central pain after SCI, the practitioners of pain management may be able to address the best treatment for those patients [17-18].

Objectives

The presence of pain in patients with SCI increases disability, depression, and reduces quality of life, particularly SCI-associated neuropathic pain. Therefore, the goals of rehabilitation and other treatment approaches in SCI are to improve functional level, sleep, mood, interaction with other people, return to normal daily activities, decrease secondary complications and enhance health-related quality of life. The purpose of this literature review is to provide an overview of treatment approaches for the management of all types of pain after SCI.

Method

This literature review is performed of the available articles up to 2017. This study has started after obtaining acceptance from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1395.1890). The articles in this paper were searched in Google Scholar, MIDLINE, Pub Med, Cochrane library (Cochrane trials), and Ovid sp. The study was performed by key words such as "pain management", "central pain", "chronic pain", "spinal cord injury", and "neuropathic pain".

The studies were examined by some criteria to select the inclusion /exclusion subjects. The articles included in this paper were in different trials like a randomized and non-randomized, controlled and non-controlled trial, double-blind, case series, and review articles. The other articles are opinions and suggestions from some authors according to their studies which also included in the current literature review. In term of participants this literature included all pain types especially those patients with chronic neuropathic pain. Moreover, this study included all types of lesions to the spinal cord injury (SCI) whether the lesion is traumatic or non-traumatic. All the levels of injuries were included whether complete or incomplete.

The treatment included in these articles are the

pharmacological, non-pharmacological treatment and a brief description to interventional treatment. Also, the ways of drug administration to relieve pain were different. The study was limited to the papers written in English language. The English language was applied where databases were allowed. Also, the literature excluded the non-human studies.

Data were extracted according to headings or titles in pain management for patients with spinal cord injury. Also, the efficacy of treatment and the level of pain reduction were recorded and included in this review.

The articles included in this paper used different tools for pain assessment. For example, in some studies pain rating was performed by using a visual analogue scale (VAS). Other studies used other tools for pain assessment like numerical pain ratings scales (0 –100), and a verbal pain rating scale (none, mild, moderate, severe, or very severe). Another group of articles for the patient's pain status used a verbal scale 1-5, also the rating of pain intensity was assessed by a scale from 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine". These tools used to determine the effectiveness of different drugs, comparisons were made of the relief obtained at the time of maximal effect after drug administration.

Results

Management of a central pain in those patients with spinal cord injury is very complicated and requires suitable evaluations of a patient's pain. In addition, the practitioners should determine the goals of therapy. So, there are many options for pain management and usually the practitioners in pain management utilize a combination of these choices to treat a refractory pain after SCI. There are different approaches available for treating pain after SCI such as medications, physiotherapy, and neurosurgical treatment.

Medications

Many medications demonstrated their efficacy for treating different types of pain after spinal cord injury. Some studies suggested that patients with spinal cord injury should start their treatment with simple analgesics like paracetamol or (NSAID).

Antidepressants act on the pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin. These neurotransmitters are involved in descending pathway of pain in the spinal cord. Tricyclic antidepressants (TCAs) which are classified as secondary amines such as (nortriptyline) and (desipramine), and tertiary amines like amitriptyline and imipramine showed efficacy in reduction of pain. Because of their mechanism on both of norepinephrine and serotonin inhibition reuptake, the tertiary amine (TAC) showed more efficacy in reduction of pain. Whereas, secondary amines (TCAs) also are effective, but they are less effective than the tertiary amines, because their action is selected only on norepinephrine neurotransmitter. Also, (TCAs) are found out to act on histamine H1-receptor affinity (associated with sedation) [19]. Some antidepressants like (venlafaxine) and (duloxetine) introduced later also are reported to have greater analgesic effect on neuropathic pain and have less side effects [20]. In contrast, the drugs that act on serotonin receptors (SSRIS) are ineffective in treating neuropathic pain [19-20]. But some studies mentioned that antidepressants are accompanied by serious side effects like

increase spasticity and urinary retention [21]. Amitriptyline and nortriptyline have the best documented efficacy in the treatment of neuropathic and non-neuropathic pain syndrome. In the second level the antidepressants bupropion, venlafaxine and duloxetine also were examined and showed some efficacy in treating pain [22]. Amitriptyline is accompanied by many side effects like dry mouth, drowsiness or tiredness, constipation, urinary retention and increased spasticity reported [23].

Antiepileptics are valuable drugs to relieve pain through their mechanism by limiting neuronal excitation and enhancing inhibition. Their action on inhibitory receptors of GABA and glycine is by enhancing binding to GABA-A₁ receptors, by blocking presynaptic GABA uptake, by inhibiting the metabolism of GABA by GABA transaminase, and by increasing the synthesis of GABA [24]. Also, the other mechanism by blocking sodium and potassium channels in that way would stop hyperexcitability of the neurons of spinal cord and then would relieve pain. There are two classifications first and second generation. Many studies reported that the second generation is more effective in treatment of neuropathic pain like (gabapentin, pregabalin, and lamotrigine). In turn the second generation of antiepileptic varied in their efficacy for treating different conditions. Other studies conducted exploratory study of pregabalin and reported a greater improvement in reducing neuropathic pain associated with sleep disturbance [5]. Recently, gabapentin was examined and was confirmed as the best treatment for both neuropathic pain and fibromyalgia, but that treatment require different doses (daily doses 1200 mg or more). Although, pregabalin and gabapentin were studied the most, other drugs such as lamotrigine, levetiracetam, sodium valproate, carbamazepine, phenytoin, oxcarbazepine and lacosamide also have demonstrated their efficacy for neuropathic pain [8,25]. Summarily gabapentin and pregabalin should be used before other antiepileptics in the SCI-related neuropathic pain. As a last resort with refractory neuropathic pain related to SCI other antiepileptic drugs may be considered. In another study gabapentin was considered as the first-line agent in acute or chronic situations followed by a tricyclic antidepressant (TCA) (amitriptyline or nortriptyline) or a weak opioid, such as tramadol, as second-line treatment. Especially, gabapentin and pregabalin were assessed in patients with SCI and neuropathic pain and were found to be beneficial [26-27].

Analgesics

Opioid administration has effects throughout the body following SCI, involving attenuation of locomotor function, facilitation of pain development, suppression of immune activation and risk of addiction. So, mu opioid receptors like morphine are considered to be among drugs that demonstrated their efficacy in treating neuropathic pain after SCI [28]. In the long term, most of patients cannot continue opioids because they would experience many dangerous adverse effects. There are a lot of side effects accompanied with opioid administration like respiratory depression, constipation, and the patients would be at risk of addiction. But some experimental trials suggested the possibility to use opioid for short-term in the acute cases of pain following spinal cord injury. Moreover, for intractable pain, trials suggested that a combination of opioid like morphine and other drugs like clonidine intrathecally produced

significantly more pain relief than placebo. The trials demonstrated that some cases of pain after SCI are difficult to treat with morphine alone, therefore the trials were done to examine a combination of morphine and other drugs like clonidine and confirmed their efficacy in relieving pain [29].

N-Methyl-D-Aspartate (NMDA) a neurotransmitter which is thought to be among the neurotransmitters that is released at the time of injury to the spinal cord. Reasonably, Ketamine which is NMDA antagonist can relieve pain, thus many trials examined its efficacy intravenously in treating pain after SCI. Some of these trials were comparative studies with other drugs or placebo. In comparison with ketamine, other for example lidocaine intravenously showed that ketamine was superior to lidocaine and demonstrated improvement in treating pain after SCI [4]. Usually, the analgesic effect (NMDA) receptors antagonist like ketamine in clinical studies and clinical practice is given by the dose limiting side effects. Therefore, the possible side effects of ketamine are sedation, dizziness, and visual distortions. But most of the patients who were examined for time under ketamine treatment experienced very disturbing side effects. The level of pain relief was satisfactory to some extent but the registered side effects limit the clinical advantage of treatment. Ketamine infusion as adjuvant to oral gabapentin was efficacious way to relieve pain by using multi-day low dose for seven days, was superior to gabapentin alone. Moreover, the analgesic effect of ketamine infusion lasted for 2 weeks after infusion. Consequently, if treatment of ketamine is continued longer than one week it results in significant response [17]. A preferred method for all patients is pain-controlled analgesia device that delivers drugs to patients whenever they need. Ketamine has been used and has demonstrated a valuable effect in managing intractable central pain [30].

Lidocaine: There is a role to sodium channels blocker like lidocaine to attenuate the pain after spinal cord injury. Different ways of administration were examined like intravenous, topical, and intrathecal administration. Anyway, the trials that examined lidocaine intravenously in comparison with other drugs like ketamine demonstrated a reduction of pain after spinal cord injury but not significantly [4]. Another study showed that lidocaine intravenously has effect on a reduction of central pain after SCI at the level of injury and also below the level of injury [31]. But the study reported many effects to intravenous administration for a long-term like toxicity when it is given alone. These studies suggested that for a better treatment we can use some agents in addition to lidocaine to relieve pain after SCI [32]. Transforaminal epidural injections with lidocaine and depo medrol were studied via trials to relieve intractable pain after SCI. The result was complete resolution in pain reduction for some patients and increase in quality of life. The injection results in reduction of pain for months [33].

Botulinum toxin A (BTA) is examined for treating neuropathic pain in patients with spinal cord injury (SCI). All participants who received medication showed an improvement in their pain and pain relief maintained for one week. Also, no side effects have been reported [34].

Tramadol is mu opioid receptors agonist which has a good analgesic effect as reported in some studies. Tramadol showed an efficacy in some recent studies which suggested the use of tramadol after gabapentin and pregabalin treatment. Tramadol is considered less dangerous in term of

dependence and abuse in comparison with opioids. Others have emphasized its use as a second-line treatment after gabapentin in patients with SCI. Studies have recommended to start treatment with low initial doses to avoid the adverse effects like dry mouth, constipation, dizziness which are reported in some cases after administration tramadol [27].

Non-Steroidal Anti-Inflammatory Drugs (NSAID) plays an important role to alleviate pain after spinal cord injury especially musculoskeletal pain. Obviously, in addition to central pain, it has a peripheral mechanism by inhibition of prostaglandin synthesis. Therefore, some studies reported its efficacy in treating musculoskeletal pain in combination with oral paracetamol [35].

Baclofen: studies emphasized that intrathecal baclofen significantly suppressed chronic pain, in addition to its effect to treat spasticity [36].

Cannabinoid receptors bind ligands such as endocannabinoid. It acts on ligand receptors that modulate a variety of physiologic processes such as pain, mood, and memory. The most common cannabinoid tetrahydrocannabinol (THC) is a cannabinoid and it is the active compound in cannabis which acts at cannabinoid receptors. This was examined to demonstrate improving spasticity and pain following SCI.

Spasticity treatment

Spinal cord injury causes injury to the upper motor neurons within the central nervous system which can lead to involuntary muscle contractions which is called spasticity. However, many studies suggested that treatment of spasticity that is associated with central pain can participate in treating pain itself. There are a variety of treatments for spasticity which are medication, physical therapy, and surgical interventions [21]. The most pharmacological treatments are antispastic medications which are administered orally or intrathecally such as baclofen, diazepam, tizanidine, clonidine, and dantrolene. Studies reported that these drugs may be associated with pain relief in addition to treating spasticity. Efficacy of these drugs is according to their mechanism. Some of these drugs which act on GABA neurotransmitters in the central nervous system reported analgesic effect in addition to treating spasticity like baclofen and diazepam. The action of baclofen is different somewhat an agonist of GABA-B receptors. When baclofen binds to GABA-B receptors both presynaptic ally and postsynaptic ally, monosynaptic and polysynaptic spinal reflexes are inhibited. Some studies reported that baclofen in addition to having an analgesic effect, they emphasized that baclofen is safe and effective for long term use without evidence for tolerance. Clonidine, an alpha-2-adrenergic agonist can bind to alpha-2 receptors, thus preventing the normal action of norepinephrine to transmit and act as a neurotransmitter and thus would participate in spasticity treatment. Tizanidine is, like clonidine, is acting (spinally and supraspinally) as an alpha-2-adrenergic agonist. thus, it acts by inhibiting the release of excitatory amino acids from the presynaptic terminals of excitatory spinal neurons. It might also facilitate the inhibitory neurotransmitter glycine. Dantrolene sodium, its mechanism in treatment spasticity is different somewhat by acting on the muscle tissue, rather than at the spinal cord level, to weaken muscles that are overexcited. It inhibits muscle action potential-induced release of calcium from the sarcoplasmic reticulum to the active myosin fibers during

muscle contraction by increasing the binding of calcium to the sarcoplasmic reticulum. Cyproheptadine is a histamine and a serotonin antagonist which is proposed to reduce spasticity through inhibition of motor neurons by neutralizing the spinal and supraspinal serotonergic excitatory. But studies have showed less efficacy in the treatment of spasticity. Tetrahydrocannabinol (THC) is the active form of Cannabis, available in the drug dronabinol. Cannabinoids have been shown to have efficacy in treating spasticity. THC is an effective and safe drug in the treatment of spasticity. At least 15–20 mg per day were needed to achieve a therapeutic effect [37]. The studies also suggested that nabilone may be beneficial to reduce spasticity in people with SCI. It is recommended to examine the drug by further trial with a more prolonged treatment period and escalating in the dose [38].

Physiotherapy treatment

It can contribute to minimize spasticity by reducing biomechanical side effect. Also, some trials suggested the electrical stimulation for both peripheral and central nerves that may participate in pain relief. The last choice for patients who are suffering from spasticity is the surgical interventions. After all these trials mentioned above, these interventions included that the ablation of sensory spinal nerve root result in blocking the sensory inputs. Also, ablation can include motor nerves which is more effective when spasticity is concentrated in muscles innervated by the same nerve trunk [39].

A Combination drug therapy

Treatment of chronic pain following SCI is difficult to treat in many cases. Moreover, the combinations of drugs might contribute to reduce the potential doses and that would be beneficial to minimize the adverse effects. Therefore, studies are performed to examine some combinations of drugs orally or intrathecal injection to get better treatment for pain after SCI. The studies emphasized that a combination of drugs can give significant efficacy in pain reduction more than their constituents. Engaging more than one relevant target by a combination of drug therapy may significantly improve pain management in SCI patients [40].

For instance, in refractory pain and spasm, studies reported that the effective way is intrathecal morphine with combination of baclofen or clonidine that may result in a good analgesia for spasticity and pain. Also, some simple analgesics like (NSAID) have analgesic effect but not as well as epidural injection of morphine with clonidine or baclofen. But some of these combinations did not demonstrate a significant efficacy in treating pain like lidocaine in combination with glucocorticoids [41]. A combination of gabapentin or nortriptyline with oral morphine showed a superior analgesic efficacy. Another study demonstrated that the efficacy of oxycodone - pregabalin combination was superior to either drug alone [42]. Also, there are some drugs that have demonstrated their efficacy like oral lithium, trazodone, duloxetine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine and citalopram. But these drugs, alone did not demonstrate their efficacy. For better treatment a combination of some these drugs may be needed. Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth as the most frequent adverse effects [42].

Non-pharmacological treatment

Experts develop many drugs to treat pain after spinal cord injury; however, they have significant side effects. Therefore, many trials have suggested many procedures that accompanied drug administration to relieve pain with smaller doses and minimizing the side effects in the same time. Physiotherapy, exercise, acupuncture, hypnosis, massage, and transcutaneous electrical nerve stimulation (TENS) may be effective and can be a complement to the pharmacological therapy to reduce nociceptive and mixed pain after spinal cord injury. TENS was examined by a prospective study and the efficacy was effective somewhat also a massage, acupuncture, and physiotherapy have demonstrated their efficacy [43-44].

Exercise may participate in pain treatment and partially alleviating many of the secondary health complications associated with SCI and promote a better quality of life [14]. Some physiotherapy treatment may be effective and can complement to pharmacological treatment. Some studies indicated that the role of exercise in treating pain after SCI is promising [45]

Transcutaneous electrical nerve stimulation (TENS); was examined by prospective study to evaluate its effect in treating pain after SCI. TENS demonstrated by clinical studies through its mechanism, when, delivered electrical current, some people experienced less pain. This may be because the electricity from the electrodes stimulates the nerves in these affected areas and sends signals to the brain that block pain signals. Another theory is that the electrical stimulation of the nerves may help the body to produce natural painkillers called endorphins, which may block the perception of pain [43-44].

Acupuncture and massage; It has been reported that acupuncture and massage therapy may participate in relieving pain after SCI. Treatment by massage also may be beneficial, and at the same time does not cause discomfort for the individuals with SCI and therefore stimulation in areas with allodynia or unpleasant feelings from touch would be avoided [46]. Therapeutic effect of acupuncture is the stimulation of specific points (acupoints) near the surface of the body. According to the mechanism of acupuncture some studies debate its efficacy, where physiological therapy depends on the pathological state of each patient. Therefore, its efficacy is different among patients [47]. Acupuncture has been studied by non-human trial and has demonstrated therapeutic efficacy to relieve chronic pain after SCI. The analgesic efficacy by inhibiting the production of superoxide anion, which in turn acts as a modulator for microglial activation [48].

Surgical interventions

Surgical procedures may be the last resort to treat pain. Intrathecal pump is surgically implanted in the subcutaneous tissue of the abdominal wall. They are indicated in individuals who do not respond to administration of medications or to other approaches or who have had intolerable side effects from medications. Intrathecal baclofen should be considered prior to surgical intervention. Also, many drugs via intrathecal pump can be used for spasticity and pain relief. Functional neurosurgery has the ability for the treatment of SCI. The surgical procedures might immediately relieve some of the many visceral and sensory-motor deficits and has the potential to produce some useful degree of reversal of the underlying neurodegeneration [49].

Dorsal Root Entry Zone (DREZ); is a neurosurgery procedure for the treatment of chronic intractable pain due to deafferentation. The surgery was effective for those patients with intractable chronic pain after spinal cord injury. Indeed, the results were interesting enough because pain relief was complete for most of the patients [50].

Decompression surgery: after spinal cord injury many fragments of bones or disk cause compression on the neuronal tissues in the site of injury. These fragments result in many complications such as chronic pain that accompanied those patients with spinal cord injury. Therefore, the surgical decompression is done to decompress the neural canal from fragments of bone or disk. Some studies demonstrated the efficacy of this procedure by anterior decompression of the thoracolumbar spine. The studies indicated significant relief of chronic pain and some improvement in neurological functions for traumatic and non-traumatic injury [51].

Epidural injection; Several studies have been conducted to evaluate the efficacy of epidural injection to alleviate chronic pain and the spasticity associated with pain after SCI. Clinical trials showed that spasticity and pain were dramatically relieved by epidural steroid injection [52].

Intrathecal injections; have demonstrated their efficacy in treating pain after spinal cord injury. Some of these drugs may be used alone or in combination with other drugs which indicate more efficacy. For example, intrathecal baclofen and botulinum toxin injections (BTA) in combination appeared to be safe and effective through a clinical trial conducted on patients with spasticity and pain [53]. In a novel clinical study, the combination of intrathecal ziconotide and hydromorphone was examined for patients with neuropathic pain. This combination indicated a significant therapy for chronic pain after SCI [54].

Conclusion

Several drugs have a great effect for relieving different types of pain after SCI. For, neuropathic pain which is the most common after SCI, drugs like (gabapentin, pregabalin, amitriptyline, nortriptyline) have demonstrated their efficacy and should be used before other drugs. Other drugs, lamotrigine, levetiracetam, sodium valproate, carbamazepine, phenytoin, oxcarbazepine, lacosamide, bupropion, venlafaxine and duloxetine have more efficacy and less side effects and considered the second choice for treating neuropathic pain after SCI if first line is not sufficient.

Other drugs have effects on nociceptive more than neuropathic pain like ketamine, tramadol and NSAIDs. Opioid can be used for neuropathic pain but not for a long time.

For intractable pain, a combination of drugs can be used for both spasticity and pain like baclofen and morphine. Also, there are some approaches that may be helpful in combination with drugs to reduce the doses and side effects like TENS, exercise and acupuncture. If these treatments are not sufficient, injections can participate in treating pain for months, especially neuropathic pain and spasticity. The last resort for the patient with chronic pain after SCI is neurosurgical approach which can relieve pain and demonstrate its effectiveness like decompression surgery.

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