Chapter 14
Mechanisms-Based Pain Therapies

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Abstract Chronic pain is a prevalent disease with high impact on public health and individual's quality of life. Understanding the complex mechanisms and causes of pain is crucial for precise diagnosis, adequate management, and better patient outcomes. As we deepen our knowledge, new therapeutic targets and strategies are expanding and becoming more mechanism-based. Current mechanism-based therapies include approaches to modulating the transduction, conduction, transmission, perception, and adaptation of pain through pharmacological, interventional, surgical, physical/psychological behavioral treatments. Increasing evidence suggests that some of these treatments can not only alleviate pain symptoms but also control disease progression by modulation of inflammation and neuroinflammation.

Keywords Acupuncture · Cognitive-behavioral therapy · Electrotherapeutics · Integrative therapy · Interventional therapy · Multimodal therapy · Nerve blocks · Nerve ablation · Peripheral nerve stimulation · Pharmacotherapy · Physiotherapy · Spinal cord stimulation · Transcutaneous electrical nerve stimulation (TENS)

14.1 Introduction

Chronic pain affects approximately 50 million Americans and contributes to an estimate $560 billion per year in health care costs (Cheng et al. 2020; Dahlhamer et al. 2018). Despite the scientific advances and better understanding of the

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pathophysiology of chronic pain over the past decades, the management of chronic pain remains challenging. Chronic pain can be a result of the dysfunction of multiple disease processes involving complex neural components such as peripheral nerves, the spinal cord, and higher brain centers (Vardeh et al. 2016). For a given pain condition, different pain mechanisms can be present simultaneously (e.g., nociceptive, nociplastic, neuropathic). The condition can also be affected by the patient's comorbidities, gender, genetics and epigenetic factors, and psychosocial factors (Mills et al. 2019). Thus, identifying the exact mechanism involved can be challenging or even impossible due to limitations in our understanding of the pain conditions. Consequently, the treatment is frequently guided by the diagnosis and symptoms' characteristics (Cohen et al. 2021). Furthermore, therapies may lack specificity, have different mechanisms, and act on several targets causing unwanted side effects. Hence, it is fundamental to thoroughly assess the patient and accurately define the diagnosis and differential diagnosis, taking into consideration of the anatomy, cellular and molecular mechanisms, genetic implications, and the influences of biopsychosocial factors as anxiety, depression, social economic status, and pain catastrophizing (Cheng 2018; Cheng et al. 2020). Whenever possible, mechanism-based therapy for pain should be the guiding principle for pain management and pain research. Currently, a patient-centered, multimodal, and integrated approach is the best practice for optimal clinical outcomes (Cheng 2018; Cheng et al. 2020). In this chapter, we concisely review the commonly used and mechanism-based therapies that include pharmacological treatments, interventional procedures, surgeries, and physical and cognitive behavioral therapies (PT and CBT).

14.2 Pharmacological Therapies

Understanding the underlying pain mechanism is important in order to guide selection of medications for optimal pain relief. For example, neuropathic pain occurs when there is a lesion within the somatosensory nervous system leading to ectopic activity by voltage-gated sodium channels and transient receptor channels causing pain. Thus, medications that target and modulate those channels such as carbamazepine and lidocaine have a role on the treatment. Nociceptive pain is associated with nociceptor activation by an inflammatory process and can be treated by using non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor inhibitors (Scholz and Woolf 2002). Central mechanisms of pain are therapeutic target as well. When the peripheral noxious input reaches the spinal cord dorsal horn, there is release of substance P and glutamate into the synaptic cleft. Glutamate receptors such as N-methyl-D-aspartate (NMDA) and a-amino-3-hydroxy-5-methyl-4 isoxazolepropironic acid (AMPA) receptors play a role in the transmission of pain signals to supraspinal centers and in central sensitization of pain at the spinal cord level. Compromise of spinal inhibitory effects by GABAergic or glycinergic interneurons in the spinal cord is another mechanism of central sensitization. Furthermore, activation of immune cells (microglia) and glial cells (astrocytes) also contributes to

central sensitization through cytokine/chemokines release. Moreover, reduced descending inhibitory control from supraspinal centers may also contribute to central sensitization. Inhibiting the reuptake of neurotransmitters necessary for this path by antidepressants or NMDA receptors antagonists can lead to pain relief (Rekatsina et al. 2020). Multiple mechanisms may be present simultaneously in different pain conditions so that anti-inflammatory drugs, commonly prescribed for nociceptive pain, might sometimes work for a neuropathic condition and a membrane stabilizer, such as antiepileptic drugs, might improve postsurgical pain (Scholz and Woolf 2002).

The commonly used medications include local anesthetics, NSAIDs, anticonvulsants, antidepressants, muscle relaxants, opioids, and ketamine, among other drugs. The therapeutic targets are summarized in Table 14.1, while the guiding principle for selection of drugs are shown in Table 14.2. The mechanism of action of the local anesthetics is through a reversible blockade of voltage-gated sodium channels, inhibiting action potential propagation (Hermanns et al. 2019). NSAIDs reduce inflammation by inhibiting the COX enzyme, responsible for catalyzing the conversion of arachidonic acid into prostaglandins. The NSAIDs are divided into selective (COX-1) or non-selective (COX-2), with celecoxib representing a unique COX-2 selective medication that has decreased gastrointestinal symptoms (Bovill 1997). Anticonvulsants medications are membrane stabilizers that block calcium or sodium channels. Those channels play an important role in peripheral and central hyperexcitability (Sills and Rogawski 2020). Most muscle relaxants act centrally, activating alpha-2 adrenergic receptor and presumably increasing presynaptic inhibition of motor neurons (tizanidine) or inhibiting 5-HT2 receptor (cyclobenzaprine), improving muscle spasms (Coward 1994; Kobayashi et al. 1996). Baclofen may cause muscle relaxation via activation of GABAB receptors. Opioids activates mu, kappa, or delta opioid receptors to produce analgesia. Those receptors are coupled with G1 proteins, and the resulting effect is mainly inhibitory with a resulting hyperpolarization and reduction in neuronal excitability (Bovill 1997). There are multiple classes of antidepressants used in pain management including serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine and tricyclic antidepressants (TCAs)), selective serotonin reuptake inhibitors (e.g., fluoxetine) and selective norepinephrine reuptake inhibitors (e.g., tapentadol). These medications have inhibitory influence on nociceptive transmission through enhancing the descending bulbospinal inhibitory pathway (Fishbain et al. 2000). Ketamine is an anesthetic used to manage refractory chronic pain through its action inhibiting the NMDA receptors (Pickering et al. 2020). Many of the medications have a complex mechanism, frequently acting in multiple sites. For example, tramadol is a mu opioid receptor agonist but also inhibits serotonin and norepinephrine reuptake; methadone is a Mu opioid receptor agonist and a NMDA receptor antagonist; and gabapentin blocks voltage-gated calcium channels and modulates other targets such as transient receptor potential channels and NMDA-receptors.

The search for new pharmacotherapies continues due to limitations of the current treatments, such as lack of efficacy or undesirable adverse effects. Recently, oliceridine, a biased opioid medication, was Food and Drug Administration

Table 14.1 Therapeutic agents in clinical practice

Therapeutic target/ mechanisms	Representative drugs
μ opioid receptor agonists	Opioids: Morphine, Hydrocodone, Hydromorphone, Methadone, Fentanyl, Tramadol, Tapentadol
Cyclooxygenase (Cox-1 and Cox-2) non-selective inhibitors	Meloxicam, Ibuprofen, Naproxen
Cox-2 selective inhibitor	Celecoxib (NSAIDs)
Voltage-gated sodium channels: non-selective blockers	Antiepileptic drugs: Carbamazepine, Oxycarbazapine; Local anesthetics: Lidocaine, Bupivacaine, Ropivacaine
Voltage-gated calcium channels: $Ca_V2.2$ blocker	Ziconotide (used intrathecally for cancer and chronic non-cancer pain)
Ca^{2+} channel $\alpha 2\delta 1$ subunit blocker	Gabapentinoid: gabapentin, pregabalin (Antiepileptic drugs)
TRPV1 agonists	Capsaicin, Resiniferatoxin (RTX)
NMDA Receptor antagonist	Ketamine, a dissociative anesthetic
5HT 1B/D agonists	Triptans for Migraine
5HT/NE transporter, serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine (Antidepressants); Tramadol, Tricyclic antidepressants: Amitriptyline, Nortriptyline, Desipramine, etc.
5HT transporter, serotonin selective reuptake inhibitors (SSRIs)	Fluoxetine (alleviation of nociceptive pain, and attenuation of opioid tolerance and dependence)
Norepinephrine transporter, Norepinephrine reuptake inhibitors (NRI)	Tapentadol
Adrenergic α2 receptor agonist	Tizanidine (muscle relaxant)
5HT2 receptor antagonist	Cyclobenzaprine (muscle relaxant)
Synaptosome-associated protein (SNAP-25)	Botulinum toxin A
Vesicle-associated membrane protein (VAMP)	Botulinum toxin B
CGRP receptor monoclonal antibody	Erenumab for migraine headache prevention
CGRP monoclonal antibodies	Fremanezumab, Galcanezumab, and Eptinezumab for migraine headache treatment and prevention
TNF-α inhibitors	Infliximab, Adalimumab, Etanercept, Golimumab, and Eertolizumab for rheumatoid arthritis (RA), juvenile arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, ulcerative colitis (UC), and Crohn's disease

(FDA)-approved for the management of acute pain in controlled settings for its selectivity for the mu-receptor and reduced side effects due to low potency for beta-arrestin recruitment (Markham 2020; Tan and Habib 2021). Also, biologic therapy through the use of monoclonal antibodies (mABs) takes advantage of its high

Table 14.2 Selection of therapeutic agents in clinical practice

Types of pain	Nociceptive	Neuropathic	Nociplastic
Mechanisms	Nociceptor activation by inflammatory process	Lesion of the somatosensory nervous system leading to ectopic discharge	Immune and inflammatory processes leading to peripheral sensitisation and central sensitisation
Examples	*Somatic*: bone fracture, metastases, muscle spasm, osteoartrhitis, postoperative pain, burns	*Central*: spinal cord injury, stroke, Parkinson's disease, multiple sclerosis	Fibromyalgia, irritable bowel syndrome, complex regional pain syndrome type 1, temporomandibular (TMJ) disorder
	Visceral: cholecistitis, nephrolithiasis, angina, mesenteric ischemia, cancer	*Peripheral*: Diabetic neuropathy, postherpetic neuralgia; trigeminal neuralgia, CRPS-2, chemotherapy-induced neuropathy	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Y	?	Y
Analgesics (e.g. acetaminophen)	Y	Y	Y
Anticonvulsants	?	Y	Y
Antidepressants		Y	Y
Opioids	Y	?	?
Image guided injections	Y	Y	Y for CRPS-1 and TMJ pain
Neuromodulation		Y	Y for CRPS-1
Exercise	Y	Y	Y
Behavioural interventions	Y	Y	Y

affinity and specificity for predetermined ligands or targets in pain transmission and neurogenic inflammation with reduced adverse effects. Calcitonin gene-related peptide (CGRP) binds to calcitonin-like receptors and activates the cascade involved with nociceptive transmission. Several mABs against CGRP or CRRP receptors have been successfully utilized in clinical practice for prophylaxis and treatment of headaches based on strong evidence provided by high-impact clinical trials. Another therapy frequently used in the management of migraine headaches is botulinum toxin, which involves multiple and complex mechanisms in the peripheral and central nervous systems including reducing expression of critical pain-related the channels and receptors and inhibiting secretion of neurotransmitters that are related to peripheral and central sensitization (Matak et al. 2019; Sim 2011).

Emerging new molecular targets are under investigation or in clinical trials. For example, anti-nerve growth factor (anti-NGF) antibodies are a promising therapy for osteoarthritis with studies showing improved pain control and function; however, meta-analyses of clinical trials identified adverse effects in patients treated

with tanezumab (Sánchez-Robles et al. 2021). The transient receptor potential ankyrin 1 (TRPA1) has a major role in pain and several studies have showed its role in the inflammatory and immune response. Despite exciting preclinical findings, clinical trials had disappointing pharmacokinetics and pharmacodynamic features (Souza Monteiro de Araujo et al. 2020). Other analgesic target is the voltage-gated sodium channel Nav1.7, but human data so far has been disappointing in chronic pain conditions (Nguyen and Yarov-Yarovoy 2022).

14.3 Non-pharmacological Therapies

Acupuncture is part of the traditional Chinese medicine and has been used for more than 3000 years. It provides pain relief by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms, include endogenous opioids, serotonin, and norepinephrine. Endogenous opioids desensitize peripheral nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord. Serotonin and norepinephrine may decrease spinal NMDA receptor subunit GluN1 phosphorylation (Zhang et al. 2014). Activation of the descending inhibitory pathways may also contribute to acupuncture analgesic effects. A placebo effect may also account for some of the analgesic effects. Functional magnetic resonance imaging (MRI) studies have identified signal changes in the brain regions associated with nociceptive processing and pain perception (e.g., insula, thalamus, median prefrontal cortex); however, the available data shows no difference between verum and sham acupuncture group. Nevertheless, it has been shown that the procedure provided pain relief in many painful conditions. Based on favorable benefit/risks ratio and low cost, the procedure is among the treatments recommended for low back pain by the American College of physicians (Coutaux 2017; Ezzo et al. 2000).

The transcutaneous electrical nerve stimulation (TENS) is a non-invasive, inexpensive, self-administered technique to relieve pain. TENS techniques include conventional TENS, acupuncture-like TENS and intense TENS. Clinical experience and systematic reviews suggest that TENS is beneficial for several types of chronic pain and possibly for acute pain as an adjunct to pharmacotherapy. The mechanisms of TENS are to selectively activate large diameter non-noxious afferents (A-beta) to reduce nociceptor cell activity and sensitization at a segmental level in the central nervous system. Pain relief with conventional TENS is rapid in onset and offset and is maximal when the patient experiences a strong but non-painful paresthesia beneath the electrodes (Johnson 2007).

14.4 Interventional Procedures

Interventional techniques for pain management have increased significantly in the past 20 years. These procedures can be diagnostic (e.g., facet medial branch block) and/or therapeutic (e.g., radio frequency ablation [RFA]) and randomized studies showed that when these techniques are performed under a multimodal approach, the outcome is better compared to the injections alone (Cohen et al. 2014). Intraarticular injections of corticosteroids, hyaluronic acid, or blood-derived products aim to target the inflammation at several levels of the cascade, restore lubricant and shock-absorbing effect and reduce synovial inflammation, and deliver a broad spectrum of growth factors and other specific molecules to the injury site, respectively (Ayhan et al. 2014). Guidelines recommend intraarticular steroid injection for inflammatory disease such as osteoarthritis that affects large and medium joints; however, frequent injections may cause decrease in cartilage volume (Cohen et al. 2021). Nerve blocks with local anesthetic with or without steroid aim to reversibly block the nociceptive afferent fibers and decrease the inflammation process. Interestingly, the clinical response for the blocks often far outlasts the pharmacological effect of the medications and a central or systemic effect might also be present (Caracas et al. 2009; Gracely et al. 1992). Epidural steroid injection (ESI), for example, is routinely performed for conditions such as radiculopathy. A recent meta-analysis showed that the use of ESI for lumbosacral radicular pain is more effective compared to conservative measures (Yang et al. 2020) and only low-quality data supports the procedure for non-radicular pain(Cohen et al. 2013). For cervical conditions as disc herniation or stenosis, level II evidence supports ESI for long-term pain improvement (Manchikanti et al. 2015). Nerve ablation is a modality that irreversibly blocks the nociceptive afferent signal and possibly provides a longer-term relief of joint pain or peripheral neuropathic pain conditions through radio frequency ablation (RFA), cryoneurolysis, chemoneurolysis (phenol or alcohol), and balloon compression. RFA is the most frequently performed procedure in this category and targets sensory nerves without a significant motor component (alpha fibers). It is most commonly used to provide longer-term pain relief from facet, sacroiliac, knee, and other joints depending on the technique applied and patient characteristics (Cohen et al. 2021). The duration of pain relief is believed to be limited by re-innervation of the target region through regeneration of the ablated nerve fibers and/or sprouting of adjacent nerve fibers.

14.5 Surgical Approach

There are multiple surgical procedures designed for chronic pain conditions, particularly involving large joints and the spine. Large joint procedures such as total knee or hip replacement not only can reduce pain but also improve functionality. Studies showed that up to 38% of the patients continued to have post-surgical pain

after the arthroplasty (Fletcher et al. 2015), most likely due to neuropathic, nociplastic, or a central component of the pain. Spine surgeries, such as laminectomy, foraminotomy and discectomy, aim to decompress specific nerves, decrease the inflammatory process, and improve pain and other symptoms. The outcomes are variable depending on many factors. For example, in a systematic review, low-quality evidence supported surgical decompression for lumbar disc herniation compared with non-surgical management for pain improvement at 6-month and physical functions at 1-year follow-up (Chen et al. 2018). For lumbar discogenic pain, no significant differences in disability scores were identified between patients who had lumbar fusion versus the nonoperative group (Chen et al. 2018), suggesting that lumbar fusion is not indicated unless there is a significant spinal instability. A systematic review showed that patients with degenerative cervical myelopathy that underwent surgical management had similar functional outcomes compared to the non-surgical group, although those managed conservatively had higher rates of hospital admission and treatment for spinal cord injury (Rhee et al. 2017).

14.6 Neuromodulation

Neurostimulation is a growing field in pain management and is discussed in detail in Chap. 14. This modality of treatment provides pain relief by electrical modulation of the nervous system through spinal cord stimulator (SCS), dorsal root ganglion stimulator (DRG) and peripheral nerve stimulator (PNS), among others. Here, we briefly highlight the major advances of neuromodulation in recent years.

SCS is most frequently used to treat failed back surgery syndrome (FBSS), non-surgical refractory back pain (NSRBP), painful diabetic neuropathy (PDN), and complex regional pain syndrome (CRPS). Electrode(s) are implanted percutaneously or surgically in the posterior epidural space in the thoracic or cervical spine to target the dorsal column of the spinal cord. The mechanisms of action are complex and not fully understood, although it is initially based upon the gate control theory. More recent studies indicate that both neuronal and non-neuronal mechanisms may contribute the therapeutic effects. For example, RNA sequence analysis studies reveal that SCS-induced differentially-expressed genes (DEGs) are concentrated around signaling pathways in the immune functions mediated by microglia, and synaptic signaling/cell-cell signaling/trans-synaptic signaling between neuronal cells (Stephens et al. 2018).

In recent years, several high-impact randomized controlled trials (RCT) provide strong evidence supporting the efficacy of SCS in several refractory pain conditions. In failed back surgery syndrome, two RCTs observed significant pain improved when SCS was compared to conservative medical treatment alone (Kumar et al. 2007, 2008). However, in these studies SCS was less effective to manage low back pain compared to leg pain. More recently, new modalities have been used to address low back pain through multicolumn leads and new stimulation modalities such as high-frequency (10 k Hertz) stimulation (HF-10), burst stimulation, and close-loop

stimulation with better outcomes (Moisset et al. 2020). A RCT demonstrated superiority of high-frequency (HF-10) SCS over traditional SCS with higher success rates (~80%) in reducing both the back and leg pain by at least 50% in patients with FBSS (Kapural et al. 2015). This effect was sustained in 24-month follow-up (Kapural et al. 2016). HF-10 SCS was further studied for non-surgical refractory back pain in a RCT that demonstrated similar efficacy in follow-up over 12 months, providing evidence for durability of the therapy to improve pain, physical function, quality of life, and opioid use (Kapural et al. 2022). Notably, in a recent RCT, HF-10 SCS has been demonstrated to achieve 85% success rate in reducing pain by at least 50% in patients with painful diabetic neuropathy (PDN), a common and debilitating complication of diabetes, in contrast to conventional medical management (CMM), which has a success rate of 5%.

Closed-loop SCS takes advantage of recording and utilizing evoked compound action potentials (ECAP) from spinal cord stimulation to automatically control the stimulus intensity of SCS through a closed-loop feedback mechanism, thereby to deliver stimulation at therapeutic intensity continuously. This modality has recently FDA-approved for clinical application for patients with failed back surgery syndrome or non-surgical refractory back pain, based on a recently published RCT (Mekhail et al. 2020, 2022).

DRG stimulation has recently been studied in patients with CRPS in the lower extremity in a RCT. Specifically designed electrodes are placed in close proximity to the DRGs concordant to the involved regions of the CRPS in the leg, such as L4, L5, and S1 DRGs. The RCT demonstrated that DRG stimulation is safe, efficacious, and superior compared to SCS in managing CRPS in the lower extremities (Deer et al. 2017). PNS may be considered when the pain is restricted to one or two specific nerve distribution. More detailed information is provided in a systematic review we recently published (Xu et al. 2021).

14.7 Physical and Cognitive Behavioral Therapies

Decreasing pain and restoring function are the primary goal of physical therapy (PT). The treatment plan is delineated by the physical therapist and might include manual therapy (e.g., massage and joint manipulation), exercise, education, TENS, heat/ice, among others. Although mechanisms of PT are complex, studies have shown that clinical practice might be guided by mechanistic understanding of the particular pain condition at hand. For example, if a nociceptive-driven pain is suspected, a region-specific exercise might have a better outcome compared to a pain with a central sensitization component that may benefit more from a generalized strengthening or aerobic exercises with a focus on modulating central inhibition and excitation (Chimenti et al. 2018).

Cognitive behavioral therapy (CBT) is the most common psychological approach for patients with chronic pain and consists of evaluating and managing maladaptive thoughts and behaviors with the goal to improve emotions and coping techniques.

CBT has been studied in different pain conditions as a stand-alone therapy or combined therapy. A systematic review showed that CBT provided small benefit for reducing pain, disability, and distress in the short-term compared with treatment as usual/waiting list (Eccleston et al. 2009). Mindfulness therapy is a subtype of CBT that promotes nonreactive self-regulated awareness. It can be performed by different meditation routines and does not require a specific training (Jinich-Diamant et al. 2020). Neuro-imaging studies utilizing functional MRI demonstrated potential mechanisms supporting short and long-term pain attenuation (Zeidan et al. 2019). A systematic review found sufficient evidence across a large body of literature (59 studies, over 5000 participants) that CBT has small or very small beneficial effects for reducing pain, disability, and distress in chronic pain (Williams et al. 2020).

14.8 Multimodal Approach

Pain is determined by biological, psychological, and social factors and treatment plan should address each of these components by a multidisciplinary team. Guidelines recommend incorporating a biopsychosocial approach into individualized plans of care. Although this approach can be costly and time-consuming, the long-term benefits in terms of quality of life and function likely outweigh these issues (Steglitz et al. 2012). In addition to pharmacological and non-pharmacological measures to manage chronic pain, a comprehensive approach should also include self-care, sleep hygiene, smoking cessation, weight loss if indicated, and a healthy lifestyle. Pain-related disability is lower in patients who have an active role in their care (Steglitz et al. 2012). Exercise is the most frequently used self-management that improves deconditioning and helps weight loss, sleep, and general well-being, as discussed in Chap. 15. Exercise is more beneficial for function than pain relief and for musculoskeletal and diffuse pain compared to neuropathic pain, although it is beneficial across different pain conditions (Geneen et al. 2017). Several RCTs showed that exercising two to three times per week for 20–30 min is beneficial for pain relief and functionality (Chimenti et al. 2018).

Pain can also be the cause and/or consequence of sleep deficiency. Poor sleep quality and duration are risk factor for chronic pain. Deficient sleep can lead to hyperalgesia and exacerbation of the pain symptoms (Haack et al. 2020). Hence, focusing on improving sleep is an important part of pain management. Healthy and balanced diets might reduce inflammation and sensitization and improve chronic pain, as discussed in Chap. 15. However, there is no data favoring a specific type of diet as superior (Field et al. 2022). Educating and supporting the patient to have realistic expectation on the management of the pain condition are also important. In conclusion, given the complexity of chronic pain, successful management must be patient-centered, multimodal, and integrated through self-care combined with a multidisciplinary team approach.

It is important to point out that some of the above-mentioned treatments can not only alleviate pain symptoms but may also control diseases progression, by

modulation of inflammation and neuroinflammation. These inflammation-modulating treatments are not restricted to anti-inflammatory treatments, such as NSAIDs. They also include neuromodulation (SCS, vagal nerve stimulation (VNS)) and non-pharmacological/complementary treatments (acupuncture, TENS) (da Silva et al. 2015; Sato et al. 2014; Ji et al. 2018; Tao et al. 2020, 2021).

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