

Conservative, interventional and regenerative methods in chronic pain management

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Abstract

Pain is a complex condition that affects an individual physically, mentally and socially and in which clinicians find it difficult to cope. In particular, the impact of chronic pain on patients' lives can range from small restrictions to complete loss of independence. Therefore, there are many applications for improving the quality of life of individual and controlling the pain. In recent years, a better understanding of the physiological and chemical mechanisms involved in chronic pain has gained pain management many new treatment methods. These are starting from non-invasive treatment methods such as physiotherapy, manual therapy, emotional therapy, and progressing to more invasive methods such as spinal cord stimulation and deep brain stimulation. Although current advances have taken effective steps in chronic pain control, more comprehensive research is needed on the effectiveness of these treatments and in which situations they are used in coping with pain. In this review, we aimed to summarize current conservative and interventional multidisciplinary methods and special treatment methods used in chronic pain management and to guide clinicians in cope with pain.

Keywords: Chronic pain; conservative treatment; electric stimulation therapy; pain management

INTRODUCTION

Chronic pain is defined as pain of any etiology not directly related to neoplastic involvement, associated with a chronic medical condition or extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual (1). Chronic pain disorder is based on a complex relationship of somatic, psychological and social factors and interactions. Thus, chronic pain represents a biopsychosocial general event in which it is necessary to evaluate within a general therapeutic concept corresponding to individual components that are not tumor-dependent. Since monodisciplinary treatment methods do not adequately cope with multimodal pain events, multimodal approaches have been developed which have proven to be effective treatment methods (2). According to the guideline prepared by the American Society of Anesthesiologists, single modality interventions, as components of a multimodality approach to pain management, include the following: pharmacological management, physical or restorative therapy, electrical nerve stimulation, psychological treatment, minimally invasive spine procedures, acupuncture, ablative techniques, injections (i.e. steroids, botulinum toxin),

blocks (i.e. joint and nerve or nerve root). However, it also reported that it is not limited to these methods (1).

Table 1. Conservative, interventional and regenerative methods in chronic pain management

Conservative methods	Hot-cold agents, TENS, exercise, manual therapy, osteopathy, chiropractic, biofeedback, cognitive behavioral therapy, acupuncture, aquaterapy, yoga, high intensity laser therapy
Interventional methods	Sympathetic blocks, radiofrequency ablation, spinal cord stimulation, high frequency stimulation, deep brain stimulation, peripheral nerve stimulation
Regenerative treatments	Prolotherapy, platelet-rich plasma

In this direction, conservative treatment methods such as rest, drug treatment, physical therapy, and emotional therapy are often used to cope with chronic pain. In cases where these treatments are insufficient to cope with chronic pain; interventional methods such as steroid injections, regenerative therapies, radiofrequency therapy, nerve blocks, and even surgery are preferred. Implantable

Received: 19.11.2019 **Accepted:** 06.03.2020 **Available online:** 22.06.2020

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methods such as peripheral nerve or spinal cord stimulation and intrathecal treatments are used in chronic pain situations where these methods are also ineffective (3) (Table 1). In this review, we aimed to summarize current conservative and interventional multidisciplinary methods and special treatment methods used in chronic pain management and to guide clinicians in cope with chronic pain.

CONSERVATIVE TREATMENT METHODS

Conservative treatment methods in chronic pain include rehabilitative methods such as exercise, various physical therapy agents, aqua therapy, as well as complementary treatment methods such as yoga, manual therapy, chiropractic therapy, acupuncture, osteopathy (3). In general, rehabilitation studies have focused on reducing musculoskeletal pain and relieving pain due to movement. Firstly, physical approaches aim to reduce musculoskeletal pain and patients' dependence on analgesic and invasive methods. Second, painful structures can be supported by assistive devices that provide stabilization to improve patient independence and quality of life. Third, individual exercise programs have been shown not only to alleviate pain types, including various cancers and hematological populations, but also to improve other disturbing symptoms, such as sleep problems and fatigue that may aggravate pain (4).

Hot and cold agents

While temperature agents vary, most of them reduce pain by creating analgesia and hyperemia, modulating muscle tone, and cold agents are also used to reduce analgesic effect and tone, although perfusion reduces. Hot and cold agents are often preferred in addition to exercise or mobilization in chronic pain inhibition (4).

TENS

TENS (Transcutaneous electrical nerve stimulation); is a technique using electrical stimulators that can give pulsed current to stimulate peripheral nerve fibers from the skin by using surface electrodes (5). Stimulation of A- β primary sensory afferents weakens the transmission of nociceptive signals transmitted by A- δ and C fibers by activating inhibitory interneurons in substantia gelatinosa in the posterior horn of the spinal cord. As a result, it acts by reducing the pain message reaching the cortex. The control of pain at the pituitary level is mediated by the release of opioids and stimulation of the A- β nerve fibers acts by opening the spinal gate that facilitates endorphin release. The release of more endorphins results in a negative feedback loop that closes the spinal gate (5).

Since different types of nerves need to be activated to provide segmental or extra-segmental pain modulation; different TENS types are used by changing the pulse amplitude, frequency, duration or pattern. The most commonly used form is the conventional TENS, defined by the International Association of Pain Research as "low intensity (paresthesias), high frequency (50-100 Hz), small pulse width (50–200 s)".

Clinical studies have shown that when TENS is used alone in mild to moderate pain, it provides good results when used in combination with pharmacotherapy in more severe pain management. It has been shown besides musculoskeletal pain to be useful in chronic pain situations related of chemotherapy and cancer, as well as pain after amputation and surgery (6).

Exercise

Exercise has been reported to increase muscle strength, endurance, flexibility, reduce weight and maintain weight. It has also been shown to have many positive effects, such as reducing the risk of cardiovascular disease and thrombosis, lowering blood fat and glucose levels, improving the psychological status and sleep quality, increasing bone mineral density, reducing certain types of cancer and chronic pain (7). These include range of motion (ROM), stretching, strengthening, and general cardiovascular, endurance exercises (8). Therapeutic exercises aimed at increasing the strength and endurance of the muscles are also an application that can support treatment in analgesia in painful conditions such as the low back, knee pain, and bone tumors by supporting and stabilizing a painful body part (4). In a recent meta-analysis, it was suggested that aerobic exercise reduces pain, fatigue and depression, and these exercises should be administered 2-3 times a week and at a moderate to moderate level for at least 4-6 weeks (9).

Manual Therapy

Manual therapy techniques are skilled hand movements intended to improve tissue extensibility, increase range of motion, induce relaxation, mobilize or manipulate soft tissue and joints, modulate pain, and reduce soft tissue swelling, inflammation, or restriction. Massage, manipulation, joint and soft tissue mobilization, stretching is a method that includes techniques such as stretching (10). The mechanisms of action of manual therapy can be explained as follows: Restoring function by mechanically ensuring optimal muscle and myofascial clearance of movement; restoring biomechanical smoothness at the disc or facet level; mechanical afferent signal transduction reaching the spinal cord reduces pain sensation by gate control theory; increasing endorphin secretion, which increases the pain threshold and reduces the severity of pain. Manual medicine techniques are indicated for all problems of the musculoskeletal system, causing loss in the functional aperture of movement, which is generally defined as blockage, or showing asymmetry in the segment movement (11).

Osteopathy

It is a therapeutic approach based on the unity of the body, the potential of self-healing and the mechanism of interaction between the body's systems and function. Basically, somatic dysfunction is determined by history and palpation. In palpation, tissue change, asymmetry, limitation of range of motion and determination of sensitivity areas are aimed. It includes the evaluation of 10 body regions including lower and upper extremities,

thoracic spine, lumbar spine, sacrum, pelvis, head, neck, ribs and abdomen. It consists of seven basic techniques: high-velocity-low amplitude, muscle energy technique, soft tissue technique, counterstrain technique, myofascial release technique, lymphatic technique, cranial osteopathy technique (12). Current evidence from randomized controlled trials (RCTs) and systematic reviews of RCTs has suggested osteopathy-related methods for back pain, neck pain, sciatica, chronic obstructive pulmonary disease, irritable bowel syndrome, and various pediatric conditions (13).

Chiropractic

Chiropractic is based on the sensory, motor and autonomic disturbances and pain mechanisms caused by the direct or indirect pressure of the spinal mechanical dysfunction on the spinal nerve roots and provides treatment in this direction (14). In a 2015 survey of more than 5400 adults in the United States, more than 60% of respondents reported that chiropractic treatment was effective in chronic pain management of neck and back pain (15). Modern chiropractic applications mainly focus on spinal mechanical dysfunction and other musculoskeletal problems. Spinal manipulation is the most basic and frequently used practice in chiropractic. Chiropractic uses a wide variety of treatments to treat patients with a wide range of neuromusculoskeletal disorders and includes techniques such as manual deep-friction massage, myofascial release, neural mobilization, proprioceptive neuromuscular facilitation, and trigger point therapy (16).

Biofeedback

Biofeedback is a new alternative method for chronic pain syndromes. In biofeedback, computers and surface electrodes are used to reveal the physiological events of patients in visual and auditory forms. In chronic pain control, biofeedback works with central nervous system relaxation and increases endorphin levels and forms the neuroendocrine basis of pain control (8). Frequently recorded physiological parameters for biofeedback; muscle tension (surface electromyogram [sEMG]), near-surface blood flow (by recording skin temperature), heart rate, galvanic skin response, brain waves (EEG) and respiration. Combined sEMG and EEG biofeedback have been shown to effectively treat fibromyalgia (17).

Cognitive Behavioral Therapy (CBT)

Basically, it is a form of treatment based on the belief that individualized emotions can be changed by cognitive and behavioral techniques (18). Cognitive restructuring is used to identify and correct negative thoughts that may cause individuals to repeat negative emotions. A meta-analysis has shown a decrease in the perceived pain intensity, severity of depression, and improvement in health-related quality of life when compared to standard treatments of CBT or any other treatment (19).

Acupuncture

It is a method used to stimulate subcutaneous, intramuscular and periosteal tissue by using thin steel needles (0.2-0.3 mm) in areas with normal functioning

nerves. Acupuncture is a high-intensity stimulant that activates polymodal receptors and high-threshold, small-diameter A β , A δ and C fibers, causing inhibition of second-order nociceptive transmission cells by segmental and extra segmental mechanisms. It activates structures on descending pain-inhibiting pathways including ventromedial medulla and periaqueductal gray matter, which have collaterals reflected on many levels of the spinal cord (6). A recent study concluded that acupuncture improves conditions such as nausea and vomiting (associated with postoperative and chemotherapy), insomnia and chronic pain symptoms associated with fibromyalgia, knee osteoarthritis; nonspecific low back pain, toothache, epicondylitis, and idiopathic headache (20).

Aquatherapy

The hydrostatic pressure in Aquatherapy increases with depth and this causes a slightly higher force than normal diastolic blood pressure and, pressure which acts equally on the entire body surface of the patient helps to reduce edema. This pressure on the external surface of the body can cause overload of other senses and also a decrease in pain perception. Thanks to its effects on blood flow, it helps to eliminate metabolic wastes. Aquatherapy involves doing some exercises in the water. Similarly, the Burdenko Method, which is a current method that takes advantage of the effects of water on the human body, is a treatment method consisting of exercises performed in vertical position in water. The first step in the 6-step Burdenko method is to balance the body and all systems in water. The body must maintain adequate balance to maintain normal functioning and homeostasis, and to withstand the stresses that may occur during activities. The second step for quality movement is aimed to ensure coordination, the third step provides flexibility and the fourth step provides endurance. In the fifth step, speed and agility are targeted, enabling the patient to use the cardiovascular systems appropriately for maximum benefit. In step six powers is enhanced by increasing pelvic awareness and balancing the center of gravity on land and the floatation center in water. Chronic pain is inhibited by ensuring proper alignment of the body and reducing the strain on the joints by exercises in water (21). Various studies over the last two decades have shown that therapeutic water exercise can be a safe and effective treatment for patients with chronic low back pain. However, studies are needed to evaluate the efficacy of aquatherapy in larger populations and in different diagnoses (22).

Yoga

Yoga primarily aims at reducing pain and stress, allowing it to be re-interpreted consciously and recognizing the body. In addition inhibition of posterior hypothalamus on pain, endogenous glucocorticoid production by reducing the mechanism of action is thought to produce an increase in positive activation. It is also thought that posterior hypothalamus inhibition and decrease in endogenous glucocorticoid production effect pain and increase positive activation. The increase in parasympathetic activity

causes muscles to relax, to reduce excessive alertness, to regulate blood flow and to reduce inflammation, causing pain relief. In patients with chronic pain, yoga performs the correct energy flow, alignment and stretching through movements called vinyasa and asana, and provides relaxation, pain tolerance and increased awareness throughout the body through breathing practices and meditation (23). Randomized, controlled clinical trials have shown direct evidence of the benefits and safety of yoga in different chronic pain conditions, including low back pain, musculoskeletal pain, and headache, but the mechanisms underlying these results have not been fully established (24).

High Intensity Laser Therapy

Its use in physiotherapy has increased in recent years. The use of this type of laser has been made possible by the development of controllable emission approach laser systems to achieve therapeutic photothermal and photomechanical effects without tissue damage. Especially the pulse Neodymium Yttrium Aluminum oxide Garnet (Nd: YAG) laser has proved its usefulness and versatile effect in the treatment of various musculoskeletal diseases. High intensity laser realizes these effects thanks to its anti-inflammatory, anti-edema and analgesic mechanisms. Recent studies have shown that it is effective in the regenerative process of tissues, formation of bone formation, new cartilage synthesis and cartilage matrix synthesis (25).

INTERVENTIONAL METHODS

Sympathetic Blocks

Sympathetic nerve blocks play an important role in interventional chronic pain management methods. They are commonly used in the treatment of many painful conditions from headache and face pain to abdominal visceral pain, from complex regional pain syndromes to discogenic pain. Depending on the nature of the pain, these blocks can be made by applying local anesthetics (single dose, repeated or continuous), neurolytic agents or radiofrequency (26). The areas where sympathetic blockade is performed are sphenopalatine ganglia, stellate (cervicothoracic) sympathetic ganglia, celiac / splanic plexus, lumbar sympathetic ganglia, superior hypogastric plexus, impar ganglia (27).

Radiofrequency ablation (RFA)

The use of radiofrequency is mainly based on the ablation (destruction of coagulative necrosis) of tissues or destruction of tissues by storing energy in the tissue in excess of a certain amount and causing thermal damage to all living / non-living tissues. RFA can be used for various chronic pain relief and for the treatment of some tumors, percutaneously, sometimes minimally invasive in endoscopic applications and sometimes as a component of open surgery especially in tumor surgery. It can be used in facet joint, disc-induced spine pain, sacroiliac joint, knee and other joint pain, fibromyalgia or muscle and fascia pain of unknown origin (28).

Spinal Cord Stimulation (SCS)

SCS is the most common use of existing implantable electrical stimulation systems for chronic pain management. Peripheral nerve injury, complex regional pain syndrome, peripheral neuropathy (idiopathic or diabetic), central neuropathic pain from stroke or multiple sclerosis, spinal cord injury, and ischemia (heart and peripheral vascular disease) are examples of successfully treated SCS. The treatment of pain by applying electric current to the spinal cord is achieved by conducting current through the electrodes on the dorsal columns of the spinal cord to modulate the formation or processing of pain (29). For the application of SCS, an established and specific diagnosis should exist for the chronic pain, all acceptable, less invasive treatment options should be exhausted and test stimulation with temporary electrode placement should relieve the pain (30).

High Frequency Stimulation (HFS)

The term HFS is used to refer to a frequency rate of 10000 Hz compared to conventional frequencies below 1200 Hz. In a randomized controlled trial, high-frequency stimulation therapy called HF10 has been shown to provide more painkillers than conventional, paresthesia-based, low-frequency spinal cord stimulation, but HF10 does not include paresthesia (31). Although HF10 treatment has clinically proven its usefulness in chronic low back and leg pain, studies are underway to determine the efficacy of HF10 in other chronic pain conditions using conventional SCS. A randomized controlled trial of chronic low back pain has shown that high frequency stimulation therapy improves quality of life more than conventional/ tonic stimulation (32).

Deep Brain Stimulation (DBS)

DBS is a method of stimulation involving the transfer of electric current to subcortical neural targets via electrodes placed in the intracranial region. Since abnormal functioning in the periventricular and periaqueductal area and ventral posterolateral and ventral posteromedial nuclei are thought to be important in pain pathophysiology, deep brain stimulation involves stimulation of the appropriate site depending on the type of pain. Accordingly, it includes stimulation of the appropriate region according to the type of pain. Central gray matter stimulation is generally preferred in nociceptive pain, whereas sensory thalamus stimulation is often preferred in neuropathic pain. It is preferred when the drug is taken in sufficient doses and time, when it is not sufficient for chronic pain control or when the drugs cause too many side effects (33). DBS has been used in various studies in patients with failed back surgery syndrome and peripheral neuropathic pain, trigeminal neuropathic pain and phantom leg pain, and for spinal cord injury or poststroke pain. However, deep brain stimulation for spinal cord injury and poststroke chronic pain has been shown to be much less successful (34).

Peripheral Nerve Stimulation (PNS)

PNS is a method of stimulating nerves, plexuses and branches using implantable electrodes. It is frequently

used to stimulate nerves and regain function in patients with diaphragmatic palsy or incontinence, but it is also used in chronic pain management. PNS has been shown to be effective in reducing pain in chronic pain conditions as well as severe pain conditions such as occipital neuralgia, complex regional pain syndromes, pain after amputation and traumatic neuroma (35).

REGENERATIVE THERAPIES

Prolotherapy

Regenerative injection therapy, also called prolotherapy, is an interventional, regenerative method for the treatment of chronic musculoskeletal pain caused by connective tissue diathesis, where small amounts of an irritant solution are injected into painful ligaments and tendon attachment sites, adjacent joint spaces. It strengthens ligaments and other joint structures by stimulating the body's natural healing mechanisms, thereby reducing joint pain by improving joint stabilization and function (30, 36). Prolotherapy is used in a variety of musculoskeletal diseases due to ligament, tendon and joint injuries, dysfunction and osteoarthritis in axial and peripheral joints and which do not respond to other standard conservative treatments. Although the most common indication in the studies is chronic low back pain; thoracic and cervical pain syndromes, whiplash injuries, lateral and medial epicondylitis, rotator sheath or bicipital tendinosis, plantar fasciitis, coccydinine, osteoarthritis, temporomandibular dysfunction and sports injuries successful results (37).

Platelet-Rich Plasma (PRP)

Platelet rich plasma (PRP) is a plasma component obtained by centrifuging whole blood and containing a higher concentration of platelet than whole blood (38). The fact that it contains a large number of growth factors has led to the use of PRP injections in the treatment of various chronic musculoskeletal diseases. It is stated that growth factors, which are thought to have an effect on the healing process, can be used in the treatment with the effect of increasing the tendon and cartilage tissue regeneration by injecting locally instead of the lesion (38). There are different results regarding the analgesic effect of PRP. Overall, although recent research suggests that PRP has an analgesic effect, more studies are needed for reliable results in comparative analysis of data, since small study sample sizes and too many variables are involved in how PRP is prepared and administered (39).

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