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ABOUT COVER

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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Expert consensus of Chinese Association for the Study of Pain on the non-opioid analgesics for chronic musculoskeletal pain

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Abstract

Chronic musculoskeletal pain (CMP) is a common occurrence in clinical practice

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and there are a variety of options for the treatment of it. However, the pharmacological therapy is still considered to be a primary treatment. The recent years have witnessed the emergence of opioid crisis, yet there are no relevant guidelines on how to treat CMP with non-opioid analgesics properly. The Chinese Medical Association for the Study of Pain convened a panel meeting to develop clinical practice consensus for the treatment of CMP with non-opioid analgesics. The purpose of this consensus is to present the application of nonsteroidal anti-inflammatory drugs, serotonin norepinephrine reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, muscle relaxants, ion channel drugs and topical drugs in CMP.

Key Words: Chronic musculoskeletal pain; Non-opioid analgesics; Nonsteroidal anti-inflammatory drugs; Noradrenaline reuptake inhibitor; Nociceptor; Cyclooxygenase

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Core Tip: Chronic musculoskeletal pain (CMP) is a common disease seen in pain clinics. There are a variety of treatment options available for CMP, among which pharmacological treatment is considered to be a simple and effective basic treatment. The opioid crisis caused by excessive dependence on opioids for CMP treatment has drawn much attention and causes high vigilance to opioid safety in China and other countries. Therefore, the Chinese Association for the Study of Pain, a branch of Chinese Medical Association, convenes a panel meeting to provide guidance to the treatment of CMP with non-opioid analgesics.

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INTRODUCTION

Chronic musculoskeletal pain (CMP), characterized by persistent or recurrent pain in muscles, tendons, bones and related soft tissues, is a common disease seen in pain clinics. CMP involves a wide range of tissues and causes a lot of comorbidities. Sometimes the severe and persistent pain may lead to psychological disorders. CMP seriously affects patients' quality of life, and results in excessive medical cost and heavy social burden. In recent years, with population aging and social pressure caused by the modern lifestyle, along with other factors, the incidence of CMP has been increasing drastically, which highlights the significance of the treatment for CMP. There are a variety of treatment options available for CMP, among which pharmacological treatment is considered to be a simple and effective basic treatment. It is important to use the pharmacological treatment in a safe and effective way, which can be a challenge in many aspects. For example, the improper use of nonsteroidal anti-inflammatory drugs (NSAIDs) for CMP is very common in China. The knowledge on alternative drug is insufficient when NSAIDs fail to effectively relieving pain or result in intolerable side effects. In Western countries, the opioid crisis caused by excessive dependence on opioids for CMP treatment has drawn much attention and causes high vigilance to opioid safety in China and other countries. In this context, how to use non-opioid analgesics to treat CMP is of great social significance. Therefore, the Chinese Association for the Study of Pain, a branch of Chinese Medical Association, convenes a panel meeting to develop this expert consensus to provide guidance to the treatment of CMP with non-opioid analgesics.

PATHOGENESIS

CMP involves more than 150 diseases of the human locomotor system with complex pathogenesis and numerous etiology, which can be generally divided into three major categories: neuropathic, mechanical, and inflammatory^[1,2]. Nerve injury or entrapment due to various causes, muscle mechanical instability due to degenerative changes in muscles, and increased release of local inflammatory factors can, in most cases, directly stimulate nociceptors and sensitize them. Regardless of which category the CMP is, its pathological changes include local histopathological changes and systemic pathological changes, resulting in neurological dysfunction or structural changes^[3].

Similar to other types of chronic pain, peripheral sensitization and central sensitization represent the basic pathogenesis of CMP. Overexpression of the proinflammatory factors, IL-1 β , TNF- α , IL-6, and IL-8^[4], and down-regulation of the anti-inflammatory factors IL-4 and IL-10 play an important role in CMP^[5]. Persistent inflammatory reactions also cause an imbalance in the osteogenic-osteoclastic process, leading to osteophyte formation and osteoporosis^[6] as well as muscle fibrosis and/or calcification which further cause pain.

Protracted chronic pain leads to local structural changes such as sclerosis and/or softening of bones, muscle spasms, joint contractures, *etc.* which will further result in functional impairment, including motor limitation, cognitive and affective disorders such as memory loss, and anxiety/depressive symptoms^[7]. Cognitive and affective disorders cause decline in social skills and deterioration of decision-making systems. It is now clear that structural and functional abnormalities in high centers such as the anterior cingulate cortex and insular cortex may mediate cognitive and affective disorders in chronic pain, and in addition, they may cause and maintain central sensitization through descending facilitation pathways^[8]. This Synaptic plasticity makes CMP a type of chronic intractable pain disorder with affective disorders or dysfunction.

NSAIDS

NSAIDs are a class of non-steroidal drugs with antipyretic and analgesic effects. The main mechanism of action of NSAIDs is to inhibit the activity of cyclooxygenase (COX) and further reduce the synthesis of prostaglandins^[9]. There are many types of NSAIDs, which can be divided into non-selective COX inhibitors and selective COX-2 inhibitors according to their selectivity for cyclooxygenase subtypes. According to their different chemical structures, they can be divided into salicylic acids, indoles, anilines, pyrroles, enolic acids, arylacetic acids, and ibufenac, and commonly used drugs include indomethacin, ibuprofen, diclofenac, meloxicam, celecoxib, and etoricoxib. NSAIDs have good analgesic effects on mild to moderate CMP caused by inflammation.

A ceiling effect has been confirmed for NSAIDs. Dose escalation should be avoided, as well as the combination of two NSAIDs drugs. The adverse effects of NSAIDs are of increasing concern, with non-selective COX inhibitors predisposing to the risk of gastrointestinal bleeding and selective COX-2 inhibitors predisposing to cardiovascular and adverse renal effects^[10]. Therefore, in clinical practice, it is important to prescribe NSAIDs according to the approved labels and use these drugs in consideration with the general condition of the patient. NSAIDs should be used with caution or avoided in patients with previous history of upper gastrointestinal ulcer bleeding, ischemic heart disease or kidney disease.

SEROTONIN-NORADRENALINE REUPTAKE INHIBITOR

Serotonin-noradrenaline reuptake inhibitors (SNRIs) are a class of commonly used antidepressant medications with representative products of duloxetine and venlafaxine, which act as analgesic and antidepressant in CMP management. Their analgesic mechanism is to enhance the role of the descending inhibitory system of pain and reduce the uploading of nociceptive stimulation signals through the spinal cord.

A number of international studies and guidelines have shown that SNRIs have considerable therapeutic effects on various chronic musculoskeletal pains^[11,12]. The first guidance that includes duloxetine as recommended treatment option is the 2014 Guidelines for the Treatment of Knee Osteoarthritis by the Osteoarthritis Research Society International (OARSI). Duloxetine has demonstrated a better therapeutic effect

when used in combination with NSAIDs, with additional benefit in depressive symptoms^[13-15]. In a double-blind, randomized controlled study of 407 Chinese patients in 2017, the BPI pain score in the treatment group was significantly lower than that in the placebo group. The secondary efficacy endpoints such as Patient Global Impression, Western Ontario and McMaster Osteoarthritis Index (osteoarthritis index score), and CGI were also significantly improved. The treatment of pain with duloxetine was achieved by a direct analgesic effect, rather than its antidepressant effect^[16]. Forty-three to sixty-seven percent of patients achieved pain relief ($\geq 30\%$ or $\geq 50\%$ reduction in pain score, improvement in physical function, and subjective improvement) after 13 wks treatment with duloxetine (60-120 mg, qd); however, it is not recommended to continue the treatment if there is no improvement after more than 4 wks of continuous treatment.

Three randomized controlled trials investigating duloxetine for the treatment of chronic low back pain (CLBP) have concluded consistently that the study group had significantly lower pain scores and improvements in other secondary outcomes when compared with placebo groups^[17-19]. Another study showed that duloxetine was effective in reducing opioid consumption compared to other treatments^[20]. In the 2017 American College of Physicians guideline, duloxetine was listed as a treatment option for CLBP, with a moderate grade of recommendation^[21]. At present, there are few clinical studies on SNRIs for the treatment of CLBP in China that can provide clinical evidence to support their role in CLBP management.

Fibromyalgia causes extensive pain in the muscles and soft tissues in the whole body, and the cause of the disease remains unknown. Duloxetine has been shown to significantly reduce pain score in patients with fibromyalgia, with many patients achieving significant improvement during the first week of treatment, regardless of concomitant depression status at the dose of 60 mg/day^[22].

MPS is a local pain syndrome caused by aseptic inflammation of skeletal muscle. Patients are often accompanied by anxiety, depression and insomnia. SNRIs can be used as an adjuvant therapy, but there is no clear clinical evidence to support their efficacy.

Dry mouth and nausea are common among the adverse reactions of SNRIs. Other adverse reactions include dizziness, drowsiness, constipation and loss of appetite. SNRIs have a favorable safety profile when compared with NSAIDs in terms of gastrointestinal and cardiovascular adverse reactions; and when compared with other antidepressants in terms of cardiovascular risks. The incidence of adverse effects is lower when duloxetine is administered at a starting dose of 30 mg/day. The incidence of dose-related adverse effects of duloxetine at 120 mg/day is significantly higher than that at 60 mg/day dose.

MUSCLE RELAXANT

Muscle relaxants can be divided into two categories: skeletal muscle relaxant and central relaxant.

Skeletal muscle relaxants: Baclofen and dantrolene

Baclofen, which mainly acts on presynaptic GABA receptors by reducing synaptic conduction^[23]. Indication: Multiple sclerosis, muscle spasms caused by spinal cord disease, and brain-derived muscle spasms^[24]. Adverse reactions include drowsiness, sedation, nausea and hypotension. Dosage should be gradually reduced during long-term treatment^[25].

Dantrolene produces muscle relaxation effects mainly by inhibiting the release of calcium ions^[26] and can be used to treat spasms caused by upper nervous system diseases^[27], and is currently mainly used to treat malignant hyperthermia.

Central relaxant: benzodiazepines, non-benzodiazepines and tizanidine

The representative drugs of benzodiazepines in clinical practice are diazepam, oxazepam, estazolam, lorazepam, midazolam, alprazolam and clonazepam. They act mainly by elevating the inhibitory neurotransmitter GABA^[28], producing hyperpolarization effects. It has sedative, hypnotic, anxiolytic, and myorelaxant effects. A common adverse effect is excessive sedation.

The representative drug of non-benzodiazepines in clinical practice is eperisone, which acts on spinal motor neurons and skeletal muscle, relaxes muscle spasm, improves local microcirculation of blood, blocks the vicious cycle of "pain-muscle tension-local blood circulation disorder", thus improving CMP, especially in chronic

low back pain as the first-line treatment option. The most common adverse reactions are mild adverse reactions such as nausea and anorexia.

Tizanidine is an α_2 receptor agonist that acts through presynaptic inhibition of motor neurons^[23]. Indications: Neck, shoulder and low back pain, multiple sclerosis, cerebrovascular events and other types of myotonia. It has been reported in the literature that it is not recommended as a first-line drug for the treatment of chronic musculoskeletal pain. Tizanidine is known to have sedative and antihypertensive effects, and should be administered at a low dose when initiating the treatment^[28].

ION CHANNEL DRUGS

The ion channel drugs used in clinical practice include three categories: Calcium ion channel modulators (gabapentin, pregabalin), sodium channel blockers (carbamazepine, oxcarbazepine, lidocaine, *etc.*) and potassium channel openers (flupirtine), among which calcium ion channel modulators are most widely used in chronic musculoskeletal pain. Calcium ion channels play an important role in many physiological processes of the nervous system, such as the regulation of neuronal excitability, the release of transmitters at synaptic sites, synaptic plasticity, and gene transcription, all of which are achieved through the regulation of calcium influx by calcium ion channels. Calcium ion channel blockers relieve pain by inhibiting calcium influx and reducing the release of neurotransmitters, thereby reducing the abnormal excitation of pain conduction pathways^[29]. Among them, potassium channel openers have been withdrawn from market because of their hepatotoxicity^[30].

Common ion channel drugs

Gabapentin: Gabapentin was first used to control seizures and was subsequently found to have a role in the treatment of neuropathic pain as well^[31]. Its structure is similar to that of GABA, but it does not target GABA receptors and does not affect the synthesis and uptake of GABA. The $\alpha_2\delta$ -1 subunit of the voltage-gated calcium ion channel is the target site of gabapentin, and the specific binding can block the transport of α_1 units of calcium ion channels from the cytoplasm to the cell membrane in dorsal root ganglia and spinal dorsal horn neurons. In addition, the axoplasmic transport of $\alpha_2\delta$ -1 subunits from the dorsal root ganglia to the spinal dorsal horn can also be blocked by gabapentin. Gabapentin can also inhibit pain *via* other targets, such as transient receptor voltage channels, NMDA receptors, protein kinases, and inflammatory factors^[32].

The clinical role of gabapentin in chronic musculoskeletal pain is mainly for some "tunnel" syndromes such as carpal tunnel syndrome, cubital tunnel syndrome and other musculoskeletal pain caused by corresponding nerve entrapment as well as fibromyalgia, chronic nerve or traumatic body pain^[33]. Common adverse effects include vertigo, drowsiness, ataxia, and peripheral edema^[34].

Pregabalin: Like gabapentin, Pregabalin blocks the influx of extracellular calcium, thereby reducing the release of excitatory amino acids.

The clinical role of pregabalin in chronic musculoskeletal pain is also similar to that of gabapentin. The adverse reactions of pregabalin include peripheral edema, PR interval prolongation, dizziness, drowsiness, ataxia, headache, language disorder, tremor, *etc.* The adverse reactions of metabolic/endocrine system are weight gain, with an incidence of 4%-12%; elevated creatine kinase level and myoclonus are observed in the musculoskeletal system, and rhabdomyolysis has been reported in individual cases; mild and transient elevation of liver enzyme level, lack of saliva, constipation, visible thrombocytopenia, blurred vision, diplopia, amblyopia, *etc.* are infrequently reported with pregabalin.

Carbamazepine: Carbamazepine is a commonly used antiepileptic drug with membrane stabilizing potential, which can inhibit sodium ion channels in the cell membrane, reduce neurotransmitter release and neural cell excitability. It is commonly used in antiepileptic therapy and treatment for trigeminal neuralgia and glossopharyngeal neuralgia. It is not commonly used for chronic musculoskeletal pain^[35].

Oxcarbazepine: Oxcarbazepine, known as a 10-ketone derivative of carbamazepine, is a brand-new antiepileptic prodrug of its active metabolite 10-hydroxycarbamazepine (MHD)^[36]. Oxcarbazepine acts similarly to carbamazepine by blocking voltage-dependent sodium ion channels, stabilizing neuronal cell membranes, inhibiting neuronal repetitive firing and reducing synaptic impulse firing. Its clinical use is

similar to that of carbamazepine and less commonly used for chronic musculoskeletal pain.

TOPICAL DRUGS

Topical non-opioid analgesics for the treatment of CMP include NSAIDs, local anesthetics, capsaicin, and traditional Chinese medicines (TCMs). The common dosage forms are cream/emulsion, solution, spray, gel, and patch. Topical drugs penetrate through the skin directly to the affected tissue to exert analgesic effects, with the advantages of rapid onset, high local concentration, less systemic exposure and less systemic adverse effects, which make them more appropriate for long-term CMP management than oral formulations^[33,37,38].

NSAID preparations

Several CMP-related guidelines and expert consensus have pointed out^[33,37-44] that topical NSAIDs have a confirmed analgesic effect and are the most clinically well-documented and prescribed topical analgesics, which can be used as first-line treatment for mild to moderate CMP, either for local short-term treatment or as initial treatment before oral NSAIDs in combination with oral preparations for patients with moderate and severe pain. Topical NSAIDs include ketoprofen, ibuprofen, flurbiprofen, diclofenac, and indomethacin. Different dosage forms have different efficacies, which mainly depend on the skin permeation characteristics (permeability coefficient), water content, and whether it contributes to the dissolution and migration of active drugs. Generally gels are superior to other dosage forms^[45]. Some experts suggest that topical NSAIDs gel is often used in ultrasonic drug penetration therapy, during which it helps local penetration and absorption and improves the efficacy^[37]. Topical NSAIDs are well tolerated and safe to patients, and common adverse reactions are mild or transient skin irritation reactions (erythema, itching, *etc.*) at the application site.

Lidocaine preparations

Lidocaine exerts its analgesic effect by blocking peripheral nerve pain receptor-gated sodium channels and can be used to relieve mild to moderate CMP, and concomitant neuropathic pain (especially those with cutaneous hyperalgesia)^[33]. 5% gel plaster and compound ointment are commonly used, and the main adverse reaction is mild to moderate local skin irritation^[46].

Capsaicin preparations

Topical capsaicin acts on peripheral nerve axons, reducing the synthesis and release of substance P to produce analgesic and antipruritic effects. It is capable of effectively relieving neuropathic and OA pain^[47]. Patches and ointments are commonly used.

TCMs

Yunnan Baiyao (ointment, aerosol), Qingpeng ointment, Qizheng Xiaotong plaster and other topical Chinese patent medicines commonly used in clinical practice have certain effects of improving microcirculation and analgesia, but high-quality evidence are needed to support the mechanism of action and long-term efficacy.

OTHERS

Other medications used to treat CMP include: (1) Anti-osteoporosis drugs bisphosphonates^[48]; (2) Biologics such as TNF- α antagonists, IL-1 antagonists, CD20 monoclonal antibodies, and cytotoxic T cell activation antigen-4 antibodies can be used for CMP treatment caused by rheumatoid arthritis and ankylosing spondylitis^[49]; (3) Recent studies have shown that nerve growth factor may benefit CMP patients^[50]; and (4) TCM (drug and therapy) for CMP is also widely used in clinical practice.

CONCLUSION

CMP refers to persistent or recurrent pain in muscles, tendons, bones, and related soft tissues. The pathogenesis of CMP is complex, and its development involves a variety of factors, including tissue degeneration, traumatic, immune, metabolic, neurological, psychiatric and affective factors.

Pharmacological treatments are the basic treatment component for CMP, and the commonly used non-opioid pharmacological treatments are NSAIDs and muscle relaxants. Recently, the indication for the treatment of CMP has been approved for the antidepressant drug duloxetine, which is considered to be a new option for CMP management. Drugs targeted on ion channels should be considered for CMP with neuropathic pain.

In the clinical management of CMP with non-opioid drugs, the approved label indications and adverse reactions should be carefully considered before prescription. The goal is to balance the effectiveness and risk of the drugs, maximize the therapeutic effect while avoiding the adverse reactions. The pharmacological combination treatment should be designed with prudence to increase the clinical effects, and reduce the dose of individual drugs as well as potential adverse reactions.

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