REVIEW

Expert Consensus on Ion Channel Drugs for Chronic Pain Treatment in China

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Abstract: Ion channel drugs have been increasing used for chronic pain management with progress in the development of selective calcium channel modulators. Although ion channel drugs have been proven safe and effective in clinical practice, uncertainty remains regarding its use to treat chronic pain. To standardize the clinical practice of ion channel drug for the treatment of chronic pain, the National Health Commission Capacity Building and Continuing Education Center for Pain Diagnosis and Treatment Special Ability Training Project established an expert group to form an expert consensus on the use of ion channel drugs for the treatment of chronic pain after repeated discussions on existing medical evidence combined with the well clinical experience of experts. The consensus provided information on the mechanism of action of ion channel drugs and their recommendations, caution use, contraindications, and precautions for their use in special populations to support doctors in their clinical decision-making.

Keywords: chronic pain, ion channel drugs, voltage-gated calcium channels, voltage-gated sodium channel

Introduction

Chronic pain is defined as pain that persists for ≥3 months. The International Society for Pain (IASP) classifies chronic pain into two categories: chronic primary and secondary pain syndromes.[1] Currently, there is relatively few epidemiological data regarding the prevalence of chronic pain according to the IASP classification in the 11th edition of the International Classification of Diseases (ICD-11). In 2019, Wang et al[2] conducted a preliminary survey of 1545 patients with chronic pain according to the IASP ICD-11 chronic pain classification in five tertiary general hospitals in three provinces and four regions in China and found that the proportion of chronic secondary pain syndrome was as high as 98.64% (1524 cases), while primary pain only accounted for 1.36% (21 cases). Among them, the population with chronic secondary pain syndrome included 32.87% (501) patients with chronic neuropathic pain, 29.20% (445) with chronic secondary headache or maxillofacial pain, 22.57% (344) with chronic secondary musculoskeletal pain, 11.55% (176)

with chronic secondary visceral pain, 2.10% (32) with chronic cancer-related pain, and 1.71% (26) with chronic postoperative or posttraumatic pain.

Drugs are the primary treatment modality for chronic pain.[3] At present, besides traditional non-steroidal analgesics and opioids, ion channel drugs have been increasing used for chronic pain management with progress in the development of selective calcium channel modulators, state-dependent sodium channel antagonists, and similar drugs.[4–6] Recent studies have revealed that abnormal expression of voltage-dependent ion channels plays a key role in peripheral sensitivity, central sensitivity, and neuroplastic changes in chronic pain.[7,8] Ion channel drugs could inhibit the peripheral sensitization and central sensitization to alleviate chronic pain. Although ion channel drugs have been proven safe and effective in clinical practice, uncertainty remains regarding its use to treat chronic pain. To date, there have been no reference standards to guide clinical practice and no relevant expert consensus on this product, in China. In this context, we invited experts in basic and clinical medicine of pain management to develop a Chinese expert consensus and provide a reference for the standard application of ion channel drugs in chronic pain.

A panel of 15 Chinese pain medicine experts was organized by the National Health Commission Capacity Building and Continuing Education Center for Pain Diagnosis and Treatment Special Ability Training Project and a consensus meeting was held online on 20/08/2022. PubMed/MEDLINE, Embase, Cochrane, CNKI, and Wanfang electronic databases were searched to identify related publications, including systematic reviews, meta-analyses, randomized and non-randomized controlled trials, observational cohort studies, and case studies published in English and Chinese. Based on this evidence and clinical experience, the experts reached a consensus on the recommendations. For the quality and strength of evidence, the grading of recommendations, assessment, development, and evaluation (GRADE) system was used. For recommendation grading, the quality of evidence, clinical benefits and harm, cost, patient preference, and value were considered.

Mechanism of Ion Channel Drugs

Multiple complex pathophysiological mechanisms are responsible for the development and progression of chronic pain. Chronic pain can cause changes in the synaptic plasticity in the cerebral cortex, leading to augmented pain transmission. Peripheral and central sensitizations are major causes of hypersensitivity in patients and may initially be triggered by peripheral nerve injury and inflammation.[9] A reduction in the activation threshold of sensing channels induced by nerve injury, including changes in sodium and calcium ion channels, is an important mechanism that leads to peripheral sensitization.[10] The dorsal root ganglion (DRG) expresses a variety of ion channel proteins, such as sodium and calcium. After neuronal injury, a series of functional and density changes in voltage-dependent sodium and calcium channels occur on the membrane of DRG neurons, resulting in a large number of abnormal action potentials in this area, which is one of the mechanisms that cause chronic pain.[11]

Altered N-type voltage-gated calcium channel (VGCC) function in sensory neurons has been implicated in one of these mechanisms. N-type VGCCs contribute significantly to the synaptic transmission of pain signals in DRG neurons and play major roles in pain information processing by controlling neurotransmitter release from nociceptive nerve fibers and modulating synaptic plasticity at the first synapse of the nociceptive pathways.[12] VGCC opens when the body is subjected to noxious stimulation or nerve injury, and a large Ca^{2+} influx activates protein kinase C (PKC, an intracellular second messenger that plays an important role in the transmission of noxious stimuli), promoting the occurrence and development of pain. Calcium channel modulators inhibit the influx of calcium ions and reduce the release of neurotransmitters, thereby reducing the abnormal excitation of pain transduction pathways to achieve pain relief.[13] Gabapentin and pregabalin are the most frequently prescribed calcium channel modulators for neuropathic pain. Gabapentin interacts with subunits α2δ of the VGCC, which are mainly located in the neocortex, hippocampus, amygdala, and spinal cord. Gabapentin was first used for the treatment of epilepsy and is now used for treating neuropathic pain. Pregabalin is a new-generation drug based on gabapentin that has been approved for the treatment of diabetic peripheral and postherpetic neuralgia.

The voltage-gated Na + channel (VGSC) is a microporous transmembrane protein that is widely distributed on the membranes of excitable cells, such as neurons, and is mainly responsible for the transmembrane transport of Na +. VGSCs play a key role in the initiation and propagation of electrical signaling in excitable cells.[14,15] VGSCs consist of

pore-forming and auxiliary subunits. Nociceptors express multiple subtypes of α-subunits. Tissue and nerve damage leads to changes in the expression and function of α-subunits that in turn can lead to changes in the excitability of sensory neurons. Changes in the excitability of sensory neurons are thought to underlie chronic pain conditions.[16] To date, at least nine distinct sodium channel isoforms have been detected in the nervous system, and the sodium channel subtypes Nav1.3, Nav1.7, Nav1.8, and Nav1.9 are associated with various pain states.[17] They are useful analgesic drug targets for various types of pain, including neuropathic pain. Sodium channel blockers include carbamazepine, lidocaine, and bulleyaconitine A (BLA). They block different types of voltage-dependent sodium channels and inhibit overexcited sensory neurons.

Ion Channel Drugs in the Treatment of Chronic Pain Diseases
Chronic Neuropathic Pain
Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is the most common type of neuropathic pain, defined as pain lasting ≥1 month after Herpes Zoster (HZ) onset or healing, and is the most common complication of HZ. Meta-analysis data show that the annual incidence of PHN in the population ranges from 3.9 to 42.0/100,000, with PHN occurring in 9–34% of patients with HZ. At present, it is believed that peripheral sensitization and central sensitization are important mechanisms of PHN, and the up-regulation of voltage-gated calcium channel α2-δ subunit and sodium channel is the main reason for central sensitization.[18,19] Therefore, ion-channel drugs can be used as treatment options for patients with PHN. Compared with oral administration, topical administration can directly act on the target with better tolerance and compliance and fewer adverse gastrointestinal tract reactions.[20] The therapeutic status of ion channel drugs (gabapentin, pregabalin, and lidocaine plaster) in PHN has been clarified by the expert consensus.[21–23]

Recommendations: Calcium channel modulators (pregabalin and gabapentin) are first-line drugs for the treatment of PHN. In addition, 5% lidocaine patches can also be used as a first-line treatment, especially for patients who have difficulties in oral medications, such as those with dysphagia, since lidocaine has less systemic absorption, does not require dose adjustment, and is more convenient to use. Alternatively, carbamazepine is also effective in the treatment of PHN; however, the evidence for its use is limited, and its combination with other drugs is recommended. Although BLA has been recommended for the treatment of PHN, no large randomized controlled clinical studies have been conducted.

A systematic review[24] evaluated the analgesic effects of pregabalin in patients with PHN. A total of 2192 patients from seven clinical studies were included (pregabalin group = 1381, control group, 811). Pregabalin was associated with a higher percentage of 30% and 50% of pain responders, respectively, than the controls (P<0.05). Meanwhile, the pregabalin group had lower sleep interference scores and better PGIC scores compared to the control group (P<0.05). Another systematic review[25] evaluated the analgesic effects of gabapentin on patients with PHN. Seven trials involving 2039 participants were identified. A pooled analysis showed that gabapentin significantly reduced PHN-related pain compared with the placebo (P<0.001). Gabapentin is an effective and well-tolerated treatment for PHN. Lidocaine-medicated plaster in single or combined regimens can help relieve PHN pain and improve quality of life and sleep. A two-stage adaptive, randomized, open-label, multicenter, non-inferiority study[26] compared the efficacy and safety of 5% lidocaine-medicated plaster with pregabalin in 96 patients with PHN and reported that 5% lidocaine-medicated plaster is comparable to pregabalin in terms of pain relief in PHN but is better tolerated and has fewer adverse effects than pregabalin (Table 1). In patients with refractory PHN, nerve block therapy combined with lidocaine external plasters can be considered to improve the therapeutic effect.[27] Studies have shown that carbamazepine combined with other drugs has good efficacy in the treatment of PHN (Table 1). A randomized controlled clinical study[28] evaluated the clinical efficacy and safety of pregabalin combined with carbamazepine in 114 patients with PHN. The results showed that the visual analogue scale (VAS) score significantly decreased in the three groups after treatment (P<0.05) (carbamazepine, pregabalin, and combination groups), and the VAS score in the combination group was significantly lower than that in the other groups (P<0.05) (Table 1). According to a Chinese expert consensus[18] on PHN, BLA has also been used to treat PHN. However, there are only a few reports on the use of BLA in the treatment of PHN. Nevertheless, evidence from

Table 1 The Relatively High-Quality Clinical Studies of Ion Channel Drugs in Chronic Pain

Study	Population	Design	Sample	Intervention	Main Outcome
Baron R, et al, 2009[26]	Patients with PHN or DPNP	RCT	308	Patients received either topical 5% lidocaine medicated plaster applied to the most painful skin area or twice-daily pregabalin capsules.	5% Lidocaine-medicated plaster is comparable to pregabalin in terms of pain relief in PHN.
Mi Jun, et al, 2019[27]	Patients with refractory PHN	RCT	80	The control group was treated with nerve block, and the observation group was treated with nerve block combined with lidocaine gel plaster.	The VAS score and PSQI score were better in the observation group (P<0.05).
Wu YS, et al, 2016[28]	Patients with PHN	RCT	114	The patients were divided into carbamazepine group, pregabalin group and pregabalin combined with carbamazepine group.	The VAS score in combined treatment group was significantly lower than that in the other groups (P<0.05).
Joharchi K, et al, 2019[29]	Patients with DPNP	RCT	180	Patients were divided the randomly into two equal groups: Duloxetine and Pregabalin. Each patient received ten days placebo as a washout period, then blind capsules of Duloxetine or Pregabalin.	The intensity of patients' pain was improved by both drugs significantly (p<0.001), but there was no significant difference between the two groups.
Devi P, et al, 2012[30]	Patients with history of pain attributed to DPNP	RCT	152	Patients were randomized to receive Gabapentin or Duloxetine or Pregabalin.	A significant reduction in the pain score, sleep interference score, Patient Global Impression of Change, and Clinical Global Impression of Change in all three treatment groups over time (P<0.05), with no statistically significant difference between the groups. Improvements in pain scores and sleep interference scores were higher with pregabalin than with duloxetine and gabapentin.
Deng CH, 2014[31]	Patients with DPNP	RCT	74	Patients were randomly divided into observation group and control group. The observation group was treated with carbamazepine, and the control group was treated with amitriptyline.	A significant reduction in VAS scores of two groups, and the decrease of the observation group was better than that of the control group (P < 0.05).
Jiang J, et al, 2019[32]	Patients with head and neck cancer	RCT	128	Patients were randomly assigned to receive either active treatment with a flexible dose of pregabalin or placebo for 16 weeks.	38 Patients (59.4%) in the pregabalin arm achieved at least 30% pain relief versus 21 patients (32.8%) in the placebo arm (P=0.006).
Tsai JH, et al, 2023[33]	Terminal cancer patients	Single-arm study	96	Patients with neuropathic cancer pain received lidocaine transdermal patches for 3 days	The median NRS pain intensity from Day 1 to Day 3 was 4.0 with 95% CI (3.3, 5.0), 3.0 (2.5, 3.5), and 2.6 (2.0, 3.0), respectively. The difference between the median NRS pain intensities of any 2 days was significant (p<0.0001).
Li F, et al, 2014[34]	Patients with mid-late cancer pain	Non-randomized controlled study	40	Patients were randomly assigned to Group A and Group B. Group A was treated with BLA assisted to Morphine Sulfate Sustained-release Tablets, Group B was treated with Morphine Sulfate Sustained-release Tablets	The dose of morphine sulfate sustained-release tablets was significantly reduced in Group A compared to Group B (P<0.05).
Olesen SS, et al, 2011[35]	Patients with chronic pancreatitis	RCT	64	Patients were randomly assigned to groups given increasing doses of pregabalin or placebo (control) for 3 consecutive weeks.	Pregabalin, compared with placebo, caused more effective pain relief after 3 weeks of treatment (36% vs 24%; P=0.02).

Abbreviations: PHN, Postherpetic neuralgia; DPNP, Diabetic peripheral neuropathic pain; RCT, Randomized controlled trial; VAS, visual analogue scale; PSQI, Pittsburgh sleep quality index; NRS, numerical rating scale; CI, Confidence interval; BLA, Bulleyaconitine A.

large-scale clinical trials is limited. In patients with HZ pain, combination treatment with BLA is recommended to prevent PHN.

Diabetic Peripheral Neuropathic Pain

Diabetic peripheral neuropathic pain (DPNP) is peripheral neuropathic pain caused by diabetes or prediabetes. The general manifestation is symmetrical peripheral neuropathic pain mainly involving the distal extremities, which may also manifest as non-neuralgic pain or neuralgia in the brachial or lumbosacral plexus.[36] The prevalence of DPNP is 10–26%.[37–39] More than 70% of patients with DPNP have moderate to severe persistent pain, insomnia, poor quality of life, and mood disturbances, resulting in a 5-fold increase in medical costs compared to patients with diabetes.[40–42] Peripheral sensitization, central sensitization, and ion channel changes are the main pathogenesis of DPNP, and the high expression of α2-δ subunits on calcium ion channels is the main reason for central sensitization.[43] The therapeutic status of ion channel drugs (gabapentin, pregabalin, lidocaine plaster) in DPNP has been clarified in the multiple expert consensus.[21,36,44]

Recommendations: Calcium channel modulators (gabapentin and pregabalin) are recommended for the treatment of DPNP. For patients who have difficulty taking oral medications, the use of a lidocaine patch is recommended for the treatment of DPNP. Carbamazepine is recommended for DPNP treatment. The sodium channel antagonist, BLA, can also be used to treat DPNP; however, no large randomized controlled clinical studies have been conducted.

A double-blind randomized clinical trial conducted by Joharchi K[29] included 180 patients with DPNP to evaluate the efficacy and safety of duloxetine and pregabalin. The results showed that the intensity of pain was significantly improved by both drugs significantly (p<0.001), with no significant difference between the two groups (Table 1). However, in the duloxetine and pregabalin groups, 74% and 37% of patients, respectively, reported adverse drug reactions (ADRs). The discontinuation rates owing to ADRs were 19% and 7%, respectively. Accordingly, despite having the same efficacy, pregabalin was better tolerated than duloxetine. Another prospective randomized open-label study conducted by Devi P[30] included 152 patients with DPNP and compared the efficacy and safety of gabapentin, duloxetine, and pregabalin in patients with DPNP. The results showed a significant reduction in the VAS score, sleep interference score, Patient Global Impression of Change, and Clinical Global Impression of Change in all three treatment groups over time (P<0.05), with no statistically significant difference between the groups. Improvements in VAS scores and sleep interference scores were higher with pregabalin than with duloxetine and gabapentin (Table 1). A network meta-analysis comparing 5% lidocaine plaster with other related agents for DPNP pain relief showed that 5% lidocaine plaster provided comparable pain relief to amitriptyline, capsaicin, gabapentin, and pregabalin and that topical agents had fewer adverse effects than systemic agents.[45] A randomized controlled clinical study conducted by Deng[31] included 74 patients with DPNP and evaluated the clinical efficacy of carbamazepine in the treatment of DPNP. The results showed that the VAS scores significantly decreased after carbamazepine treatment (Table 1). Previous studies using BLA acupuncture point injection in the treatment of DPNP, showed that the physical pain of the total effective rate was 84%.[46]

Chronic Postsurgical or Posttraumatic Pain

The incidence of postoperative chronic pain ranges from 5–85% and varies greatly depending on the type of surgery. The incidence of phantom limb pain after amputation is 30–85%, after lumbar surgery is 10–40%, and after multiple traumas is 46–85%.[47] Central or peripheral pain sensitization is the main pathogenesis of postoperative chronic pain, and the high expression of α2-δ subunits on calcium ion channels is the main reason for central sensitization.[43] The therapeutic status of calcium ion channel drugs (gabapentin and pregabalin) in chronic postoperative or posttraumatic pain has been clarified in the multiple clinical practice guidelines and expert consensus.[48–50]

Recommendations: Gabapentin and pregabalin are recommended in combination with conventional analgesics for patients with chronic pain after surgery or trauma.

Eight studies were included in a meta-analysis, in which six gabapentin trials demonstrated a moderate-to-large reduction in the development of chronic postsurgical pain (pooled OR 0.52; 95% CI, 0.27 to 0.98; P = 0.04), and two pregabalin trials found a significantly large reduction in the development of chronic postsurgical pain (pooled OR 0.09; 95% CI, 0.02 to 0.79; P = 0.007).[51] After including 55 studies, a meta-regression was performed to assess the impact of

individual doses and frequency of pregabalin administration on analgesic efficacy. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24h compared with placebo {mean difference [95% confidence interval (CI)]= −0.38 (−0.57, −0.20), −0.47 (−0.76, −0.18), and −8.27 mg morphine equivalents (−10.08, −6.47), respectively}.[52]

Chronic Musculoskeletal Pain (CMP)

CMP refers to pain that occurs in the muscles, bones, joints, tendons, or soft tissues for > 3 months. The incidence of CMP increases annually, leading to pain and disability in older adults.[53] Lower back pain is the most common type of CMP, with an incidence of 30–40% in adults.[54] Central and peripheral sensitization are the main pathogens of CMP along with the abnormal opening of gated sodium and calcium channels and decreased regulatory ability of the spinal cord and central nervous system. The therapeutic status of calcium ion channel drugs (gabapentin, pregabalin) and sodium ion channel drugs (lidocaine) in chronic postoperative or posttraumatic pain has been clarified in the multiple expert consensus.[53,55]

Recommendations: Pharmacological treatment with anti-inflammatory drugs (NSAIDs) should be considered as the first-line therapy for patients with CMP. Ion-channel drugs can be added to or replaced to NSAIDs in patients who do not respond well or have contraindications (gastrointestinal and cardiovascular diseases). Moreover, they may be preferred in patients with marked central or peripheral sensitization. Gabapentin and pregabalin are recommended for chronic neuropathic limb pain; whereas, gabapentin is recommended for chronic lower back pain. Lidocaine plaster is recommended for treating chronic low back pain and neuropathic limb pain. BLA is recommended for the treatment of pain in the joints and soft tissues of the extremities, neck, shoulder, waist, and leg caused by intervertebral disc disease and for pain in patients with rheumatic immune diseases.

A systematic review of 15 trials (1468 participants) on pharmacotherapy for chronic pain found that gabapentin was more efficacious than the placebo (42% vs 19%) in decreasing chronic pain by 50% in patients with neuropathic pain, phantom limb pain, spinal cord injury, and other neuropathies. Lidocaine plasters block gated sodium channel transmission in nociceptors at the peripheral level. Plasters may have modest efficacy in the management of chronic pain secondary to LBP and various neuropathies.[56] An open, single-arm clinical study conducted by Liu[57] et al included 200 patients with chronic pain and evaluated the treatment of joint pain; soft tissue pain; and chronic pain of the neck, shoulder, waist, and leg caused by intervertebral disc lesions using BLA. The results showed that the total effective rate for joint and soft tissue pain was 80%. The total efficacy rate was 81%, and the VAS score was significantly lower after 1–4 weeks of treatment. BLA have dual pharmacological effects on central and peripheral analgesia, as well as immunoregulatory effects. Several clinical studies have shown that BLA have good clinical efficacy in treating osteoarthritis (OA), rheumatoid arthritis (RA), and knee osteoarthritis and can significantly reduce the VAS score.[58–61]

Chronic Cancer-Related Pain

Cancer-related pain refers to pain caused by direct aggression or indirect action of the cancer itself and various anti-tumor treatments, as well as pain due to other complications and non-tumor factors such as psychosocial factors.[62] The treatment of cancer pain is often based on the principle of indirect action.[63] Ion channel drugs can increase the analgesic effect of opioids, reduce the dose of opioids, and can be used for cancer-related neuropathological pain treatment and complementary treatment.[64,65]

Recommendations: Gabapentin, pregabalin, lidocaine, and BLA can be used for the treatment and adjuvant therapy of cancer-related neuropathic pain and can increase the analgesic effect of opioids and reduce the dose of opioids.

This randomized double-blind study included 128 patients to test the efficacy and safety of pregabalin versus placebo for the treatment of radiotherapy-related neuropathic pain. 38 Patients (59.4%) in the pregabalin arm achieved at least 30% pain relief versus 21 patients (32.8%) in the placebo arm (P=0.006)[32] (Table 1). A systematic review of 10 studies identified articles on the use of prophylactic gabapentin in patients undergoing head and neck cancer therapy. Prophylactic gabapentin appears to be a promising treatment option for preventing pain, reducing opioid use, and reducing weight loss in patients undergoing head and neck cancer therapy.[66] In a prospective, open-label, single-arm study, 5% lidocaine transdermal patches reduced the numerical rating scale (NRS) pain intensity in patients with

neuropathic cancer already receiving opioid treatment[33] (Table 1). Li[34] et al used BLA capsules combined with morphine sulfate sustained-release tablets to treat advanced cancer. The results showed that when satisfactory analgesia was achieved (VAS<3), the dose of morphine sulfate sustained-release tablets was significantly reduced in combination with BLA compared to morphine sulfate sustained-release tablets alone (P<0.05) (Table 1).

Chronic Visceral Pain (CVP)

CVP is one of the most common forms of pain reported clinically in chronic pain with an incidence of up to 20%. Visceral pain refers to pain in the body's internal organs and is often associated with various diseases such as acute and chronic pancreatitis and functional gastrointestinal diseases such as irritable bowel syndrome (IBS). Adjunctive drugs should be introduced during the early stages of pain management in the presence of central sensitization (hyperalgesia and allodynia). Currently, the main clinical applications are ion channel drugs.[67,68]

Recommendations: Gabapentin, pregabalin, and BLA are recommended as adjuvant analgesics in CVP treatment.

Both gabapentin and pregabalin have been demonstrated to reduce pain in patients with chronic pancreatitis and IBS.[69–71] In a randomized controlled trial, adjuvant pregabalin resulted in more effective pain relief at 3 weeks and was associated with improved health status in patients with chronic pancreatitis compared to placebo[35] (Table 1). BLA has been demonstrated to reduce pain in patients with CVP and IBS.[72,73]

Caution Use and Contraindications of Ion Channel Drugs
Use with Caution

Coronary artery disease or other cardiac impairments (except heart block), hypovolemia, or shock. Patients with liver and kidney dysfunction, chronic obstructive pulmonary disease, blood system adverse reaction history, diabetes, endocrine disorders, psychiatric history, newborns, premature infants, the elderly, and infirmities.

Contraindications

Patients who are allergic to ion channel drugs along with acute cardiogenic cerebral ischemic syndrome (A-S syndrome), pre-excitation syndrome, heart block (including sinoatrial, atrioventricular, and intraventricular conduction blocks), lactating women, patients with a history of myelopathic depression, patients with severe abnormal serum iron, patients with a history of hepatic porphyria, patients with severe hepatic insufficiency, and patients with acute pancreatitis should not be prescribed ion channel drugs.

Adverse Reactions and Treatment Principles of Ion Channel Drugs
Carbamazepine

Common side effects include blurred vision, dizziness, fatigue, nausea, and vomiting, which mostly occur 1–2 weeks after the treatment. Rashes, urticaria, liver dysfunction, and hypothyroidism are rare. Granulocytopenia, bone marrow suppression, arrhythmia, and liver and kidney failures are rare complications. Carbamazepine has a narrow therapeutic window and is associated with multiple adverse systemic reactions. Carbamazepine causes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis, and other serious diseases that are highly correlated with the variant alleles HLA-B *15:02 and LA-A*31:01 carried by patients.[74] Special attention should also be paid to hyperalgesia caused by carbamazepine withdrawal.[4]

Oxcarbazepine

The most common adverse effects were rash, dizziness, headache, and drowsiness. The total incidence of adverse effects was 45.22%, most of which were mild and alleviated or disappeared after 3–4 weeks. Oxcarbazepine can also cause a severe rash, such as life-threatening SJS and toxic epidermal necrolysis, with a lower incidence than carbamazepine (1 to 6/10,000 for carbamazepine vs 0.5 to 6/1,000,000 for oxcarbazepine).[75] During treatment, it is necessary to monitor for signs of depression, suicidal thoughts, or abnormal behavioral and mood changes.[76]

Lidocaine Plaster

The side effects of 5% lidocaine plaster include moderate skin reactions, such as erythema and rash. The use of lidocaine plasters should be avoided in patients taking oral class I antiarrhythmic drugs, such as mexiletine, and in patients with severe liver impairment. Intravenous lidocaine should be administered in an environment that includes monitoring and rescue conditions. Additionally, the concentration, total amount, and infusion speed of the drug should be strictly controlled. Patients who are allergic to amide local anesthetics or other ingredients in the product are contraindicated.

BIA

No drug tolerance, addiction, or adverse gastrointestinal effects were observed. Very few patients experienced transient mild palpitations, nausea, lip numbness, or palpitations. The response is transient and can be relieved after treatment.[77] The interval between the two administrations of BLA should not be < 6h. BLA should also be used with caution in patients with heart diseases, such as arrhythmia.

Gabapentin

Common adverse effects include dizziness, drowsiness, ataxia, and peripheral edema. The symptoms of withdrawal include disturbances of consciousness, disorientation, non-specific gastrointestinal reactions, hyperhidrosis, and tremors. Gabapentin dosage should be adjusted according to the patient's renal function. During the medication period, the withdrawal of gabapentin or the addition of a new treatment plan should be gradually carried out, and the time should be at least 1 week. The plasma concentration of gabapentin may increase in patients treated with morphine at the same time.[78] Even if gabapentin was administered per the prescribed dosage, the reaction rate was reduced. Therefore, individuals engaged in driving and manipulating complex machinery should use them cautiously.

Pregabalin

The adverse effects include dizziness, somnolence, ataxia, headaches, language barriers, and tremors. Pregabalin can cause peripheral edema and a prolonged PR interval and should be used with caution in patients with congestive heart failure and heart function grade III or IV. Adverse endocrine effects include an increase in body weight, with an occurrence rate of 4% to 12%. Muscular skeletal adverse effects include elevated creatine kinase levels, myoclonus, and stripe muscle dissolution. Pregabalin treatment occasionally causes mild transient increases in liver enzymes, saliva deficiency, constipation, thrombocytopenia, blurred vision, diplopia, and amblyopia.[79] The pregabalin dosage needs to be adjusted according to the patient's renal function. During treatment, it is necessary to monitor for signs of depression, suicidal thoughts, or abnormal behavioral and mood changes.[76]

Gabapentin and pregabalin are addictive, and sudden withdrawal increases the frequency of seizures and produces withdrawal symptoms, such as nausea, headache, and diarrhea. Therefore, when discontinuing the drug, the dosage should be gradually reduced for at least 1 week.

The Precautions of Ion Channel Drugs in Special Populations

Precautions for Children

Most ion-channel drugs can be used in children; however, pregabalin is not suitable for patients <17 years of age. BLA has not yet been tested as a medication in children, so it should be used with caution in children. Although hypothyroidism is a rare adverse reaction to oxcarbazepine, children <2 years of age should undergo a Meth test before initiation of oxcarbazepine treatment.[80]

Precautions for Pregnancy and Lactation

This drug is not suitable for pregnant women because it can be secreted through breast milk, and therefore, it is contraindicated in lactating women. Additionally, simultaneous use of oxcarbazepine and oral hormonal contraceptives is associated with contraceptive failure.[81]

Precautions for Elderly People

Elderly individuals can selectively use ion-channel drugs according to their liver and kidney function. However, elderly patients are more sensitive to carbamazepine because it frequently causes cognitive impairment, anxiety, confusion, atrioventricular block, and aplastic anemia. Accordingly, these drugs need to be carefully selected.[80,81] BLA has not been tested as a medication for the elderly; therefore, it should be used with caution.

Conclusion

Based on the existing medical evidence and experts' clinical experience, this consensus put forward suggestions regarding the use of ion channel drugs for the treatment of chronic pain, such as pregabalin, gabapentin, lidocaine patch, carbamazepine and BLA. At present, there is relatively abundant evidence for gabapentin, pregabalin, and lidocaine patch in the treatment of chronic pain. However, the evidence for carbamazepine and BLA is relatively limited. It is hoped that this consensus will support doctors in their clinical decision-making.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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