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Ion Channel Targets and Treatment Efficacy in Neuropathic Pain

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Abstract: Chronic neuropathic pain due to injury or dysfunction of the nervous system remains a formidable treatment challenge in spite of a growing range of medication choices. We review current clinical research supporting the use of ion channel modulators for neuropathic pain states. New modes of local drug delivery, novel Ca^{2+} channel targets, and increased choices for drugs with activity at Na^{+}channels are transforming this longstanding therapeutic strategy. Clinical decision making is increasingly informed by a more nuanced understanding of the role of voltage-gated Na^{+}channels (VGSCs) and Ca^{2+} channels (VGCCs) in the pathophysiology of nerve injury. Although holding great promise for the future, mechanism-based approaches to treatment will require greater understanding of the analgesic mechanisms of drug action and of the relationships between pathophysiologic mechanisms and clinical presentation.

***Perspective:** Treatment options for neuropathic pain targeting ion channels have grown rapidly in the past decade. An evolving body of clinical research supports the widespread use of this longstanding therapeutic strategy. Improved efficacy of ion channel modulators hinges upon further elucidation of the relationship between signs and symptoms of pain and underlying pathophysiology.*

***Key words:** Neuropathic pain, hyperexcitability, postherpetic neuralgia, diabetic peripheral neuropathy, anticonvulsants, efficacy, sodium channels, calcium channels.*

Diverse types of injury to the peripheral and central nervous system cause neuropathic pain. The neuronal hyperexcitability observed in animal models may have as its clinical correlate in humans the spontaneous and evoked pains of diseases such as postherpetic neuralgia (PHN) and diabetic polyneuropathy. Recent scientific advances offer refined descriptions of the changes in membrane channels that culminate in neuronal hyperexcitability. Because of their activity at potentially critical sites of membrane channels, medications that target ion channels are a mainstay of treatment for chronic neuropathic pain. At present, voltage-gated Na^{+} (VGSCs) and Ca^{2+} channels (VGCCs) are the primary targets of these medications.

Most of the ion channel modulators in clinical use for neuropathic pain were not developed as analgesic agents. Classifying these agents as antidepressants, antiepileptics, and antiarrhythmic medications can be confusing and limit their clinical use as analgesic agents acting at a common set of channels in neural tissue. Although a growing number of these agents from different medication classes have become available for the treatment of neuropathic conditions, alleviation of pain associated with nerve injury continues to pose a significant clinical challenge. A common finding has been that each agent provides effective relief of pain only in a minority of the patients treated. Hopefully, future advances in our ability to diagnose the underlying pathophysiologic abnormality that leads to chronic pain will allow treatments designed to target the specific molecular changes in an ion channel subtype that is responsible for the symptoms and signs in that individual patient.

Anticonvulsants (carbamazepine and phenytoin) and systemic local anesthetics (lidocaine and mexiletine) comprise the first generation of agents. They share a primary site of therapeutic action at the Na^{+} channels found in neural tissue. A newer generation of drugs, including topiramate, lamotrigine, and oxcarbazepine, have also demonstrated activity at both $Na^{+}$and Ca^{2+} channel subtypes, with fewer side-effects. Initially ap-

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proved on evidence of this latter generation's benefit as antiepileptic agents, their role in the treatment of neuropathic pain has not been uniformly demonstrated. The analgesic properties of gabapentin and the related pregabalin appear to be related to a strong affinity for a specific $\alpha_2\delta$ channel subunit. Another anticonvulsant with some evidence for analgesic effects, levetiracetam, is clearly not active at Na^+ channels and may be active at Ca^{2+} channels.

Other classes of agents include ziconotide, which was developed as an analgesic because it was found to antagonize the N-type Ca^{2+} channel. It represents one of the few successful attempts to develop an analgesic through highly mechanism-selective drug development efforts. Despite decades of widespread clinical use of tricyclic antidepressants for neuropathic pain and multiple controlled clinical trials, the recognition that the analgesic activity of these drugs may depend in part on actions at ion channel targets—especially Na^+ channels—is a recent phenomenon.

Neurobiology of Neuropathic Pain: The Role of Ion Channels

Neuropathic pain can be defined as pain caused by lesions of the peripheral or central nervous system manifesting with positive (eg, pain) and negative (eg, sensory loss) phenomena.[4] Common causes include trauma leading to nerve injury and deafferentation, toxins (eg, chemotherapy), metabolic injury (eg, diabetic neuropathy), and infections (eg, PHN). The exact mechanism by which each process results in a neuropathic pain syndrome remains unclear. However, as an example, consider axonal and demyelinating injuries, which can produce structural changes in the neuronal membrane. Changes in the membrane-bound proteins that form ion channels may alter the electrical properties of the injured neuron, called remodeling.[94] Preclinical studies of neuropathic pain suggest that the net effect of membrane remodeling is to make neurons more excitable. The tendency to action potential generation and propagation in injured primary sensory neurons can occur in the context of nerve injury.[23] Increased activity is seen both at the local site of nerve injury and more remotely in the associated dorsal root ganglia and dorsal horn of the spinal cord. These patterns of abnormal and excessive discharge are thought to account for the positive symptoms reported by patients with neuropathic pain. Positive sensory phenomena include pain, paresthesia, dysesthesia, hyperalgesia, and allodynia. There is an increasing appreciation that specific changes in ion channel type, distribution, and number are associated with the pattern of ectopic discharge and ongoing pain associated with nerve injury.[22,34,48,54]

The pathophysiologic changes that give rise to neuropathic pain span the nociceptive system from the primary afferent in the periphery to the cerebral hemisphere. There is no single unifying mechanism of neuronal hyperexcitability across the myriad neuropathic pain states nor in any specific location in the sensory pathways where the pain can be localized.[50] In some instances, variability in the type of channel expressed as a consequence of nerve injury would appear to account for not only the degree and type of hyperexcitability but also differences in ion channel medication efficacy.[24,75] For example, some clinical investigators have found that pain from peripheral sites of nerve injury may be more sensitive to Na^+ channel modulators than pain arising from lesions of the central nervous system.[40] Although it is certain that ion channels play a central role in cellular excitability, multiple processes at all levels of the neuraxis are crucial to the cellular underpinnings of neuropathic pain.

The afferent barrage from peripheral nociceptors leads, in turn, to *central sensitization*. This phenomenon encompasses the structural changes in connectivity of second- and third-order neurons in the central nervous system induced by tachykinins such as substance P and neurokinin A. In the spinal cord and at supraspinal sites, glutamate, acting at excitatory amino acid receptors (eg, NMDA), can amplify sensory input from the periphery. Expansion of neuronal receptive fields and neuronal reorganization in the dorsal horn all have been found to account for some degree of altered sensory processing.[105] Regulation of other receptor types and modulation of local or descending inhibitory pathways can affect the dynamic clinical presentations of neuropathic syndromes. Among the large number of neuroplastic changes now associated with neuropathic pain, the most amenable therapeutic target has been the peripheral ion channels implicated in ectopic discharge. However, even this relatively well studied phenomenon has not led to substantial mechanism-based breakthroughs in our therapeutic options.

Diagnostic Challenges and the Limits of Mechanism-Based Approaches

The challenge of a mechanism-based approach to treating neuropathic pain lies in the fact that the history and clinical examination do not disclose a precise neurophysiologic pain mechanism. The diagnosis of neuropathic pain rests on the demonstration of a lesion in the nervous system and the recognition of a related constellation of sensory signs and symptoms. A varied array of metabolic, ischemic, immune-mediated, and toxic insults can result in neuropathic pain. Importantly, the mechanisms of neuropathic pain in patients with the identical illness or injury may not be the same. Nor is there a single mechanism that accounts for relatively specific symptoms such as spontaneous burning pain or a physical exam finding such as allodynia. Currently, an evidence-based approach increases the likelihood of a positive treatment outcome because it can be based on a growing number of published, randomized controlled trials. However, we do not yet have the capability to include patients based on the underlying mechanism of the pain. Rather, each trial can only recruit patients based on the

particular set of neuropathic signs and symptoms in the individual patient.[30]

As such, the only plausible mechanistic approach, given our evolving understanding of pain neurobiology, depends on stratifying patients based on their response and the putative mechanisms of medications.[4] A major complication in this strategy is that, with few exceptions, the drugs in current use have multiple mechanisms of action. In addition, the available evidence for ion channel medications remains largely condition specific. The preponderance of clinical trials has investigated painful diabetic neuropathy, PHN, and trigeminal neuralgia. Few trials have attempted to parse medication efficacy by neuropathic symptom rather than by condition.

The generally modest level of analgesic efficacy with monotherapy using the current drug armamentarium for neuropathic pain is consistent with the need for a substantial improvement in our mechanism-based approach to treatment. An overview of the clinical trials in neuropathic pain suggests that a single agent offers, at best, clinically important relief in only 40% to 60% of patients and complete relief in a much smaller number.[77] When monotherapy fails to adequately relieve pain, a drug mechanism–based approach to the selection of additional treatment can be useful. This approach focuses on providing drug combinations that have complementary mechanisms of action. Unlike the situation in animal models, the multiple mechanisms of pain and associated disability that are likely to be operative in each patient can be used to further justify combination therapy on pathophysiologic grounds. However, from a practical perspective, this process of sequential medication trials is driven by serial assessment of efficacy and medication tolerability within the individual patient.

Methodological Considerations in Evaluating Treatments for Neuropathic Pain

The methodological gold standard for assessing treatment efficacy remains the randomized, double-blind, placebo-controlled trial. The comparison of differences in efficacy of the ion channel medications from different generations is complicated by the relative lack of rigor in research methods used to validate the efficacy of older medications. In particular, many of the older agents have only been subjected to testing in clinical trials with rather small sample sizes. Although larger clinical trials have increased power to determine treatment effects, there are analytical liabilities to clinical trials with both large and small sample sizes. Trials with large numbers of patients have the statistical power to reveal small, but sometimes less clinically relevant, improvements in pain. For example, to achieve statistical significance, large trials may not require that an appreciable percentage of patients experience the 30% or greater reduction in pain intensity that has been proposed as a clinically important difference in recent analytic work on benchmarks of treatment efficacy.[36] Some studies published before 1997 were small, single-center trials that may have overestimated drug efficacy in clinical practice. These studies examined only the data from patients completing the trial.[77] Intention-to-treat analyses, in which data from all randomized patients are included for the primary outcome analysis, are preferred because trial noncompleters tend to experience less benefit and more adverse events and their inclusion better reflects the realities of clinical practice.

The lack of prospective head-to-head trials comparing ion channel medications with other medications continues to hamper evidence-based selection of medications even in relatively well-defined patient populations. This renders the comparison between studies somewhat suspect. Clearly, changes in group mean values provide few data that are applicable to the individual patient. Responder analyses, such as the percentages of patients achieving greater than 30% (or 50%) reduction in pain, can offer a proxy approach for the direct comparisons of ion channel agents that have not yet been conducted.

Na^+ Channel Blockade

Alterations in the level of expression, cellular localization, and distribution of Na^+ channels are strongly associated with neuropathic pain.[22] Fluctuation in the total levels of Na^+ channel expression and the relative expression of each of the different channel subtypes contribute to hyperexcitability. The empiric analgesic efficacy of local anesthetics in clinical practice has supported this line of investigation. It is generally accepted that an *increase* in Na^+ channel density lowers the nociceptive thresholds in injured neurons. These neurons have a heightened tendency toward action potential initiation and propagation. Ion channel modulators preferentially inhibit abnormal excessive activity at ectopic foci with increased Na^+ channel density.[3] An example of such activity has been demonstrated in the decreased spontaneous activity in experimental neuromas produced by carbamazepine.[16] Blockade of the Na^+ channel preferentially impedes the upstroke where action potential initiation is most frequent. Spontaneous ectopic discharges are suppressed at much lower drug concentrations, thereby allowing normal impulse generation and propagation to continue. As a consequence Na^+ channel modulators possess a relatively large therapeutic window. Because ectopic firing is especially sensitive to Na^+ channel blockade, fatal toxicity due to failure of normal nerve conduction does not occur at drug concentrations that provide pain relief.

Local Anesthetics

The use of local anesthetics for the treatment of pain conditions dates back to the 1930s with systemic infusion of procaine for perioperative pain.[7,10] Blockade of ectopic discharges in animal models of neuropathic pain during the 1980s reinvigorated interest in this therapeutic approach. Infusions of lidocaine have been shown to relieve painful diabetic neuropathy in a portion of the patient population.[51] At least in one study, lidocaine

dose and plasma concentration have been correlated with pain reduction in a dose-dependent fashion.[37] In multiple randomized, double-blind, cross-over studies, intravenous lidocaine has proven superior to placebo in reducing the pain of diabetic neuropathy and PHN.[2,3,80] Across multiple trials and neuropathic pain states the effective dose is in the range of 1.5-5.0mg/kg.[58] There is some evidence that systemic lidocaine is more effective in treating pain associated with peripheral rather than central nerve injury.[40]

Despite this pattern of efficacy, intravenous infusion has not become widespread because it is not a convenient mode of delivery for patients with chronic neuropathic conditions. In addition, lidocaine binds nonspecifically to Na^+ channels in normal neural, gastrointestinal, and cardiac tissue, which leads to a number of unpleasant side effects. Systemic infusion with its high bioavailability enhances the liability of blocking conduction at these nonpathologic tissues. Attempts to find alternatives to lidocaine infusions have included the use of mexiletine, an orally available lidocaine congener. Although clinical results have been mixed, a prospective study in 9 patients with peripheral neuropathic pain reported a positive association between response to a lidocaine test (2 and 5mg/kg over 45 minutes) and outcome with mexiletine.[39]

Mexiletine

Mexiletine is a close structural analogue of lidocaine. As a practical alternative to repeated intravenous infusions of lidocaine, this medication appeared to offer the benefits of Na^+channel blockade in an oral form with high bioavailability. Mexiletine has been tested in several neuropathic conditions and the results have not been consistently positive. Analgesic benefit over placebo has been demonstrated in painful diabetic neuropathy and peripheral nerve injury but only at dosages in excess of 600 mg/day, and no benefit has been seen in the neuropathic symptoms associated with spinal cord injury.[14,17,21] Other trials have not demonstrated a benefit over placebo in the treatment of peripheral neuropathy but have reported benefit in some subgroup analyses that are of questionable clinical importance.[68,93] Mexiletine has not been shown to provide significant pain relief in patients with HIV-associated neuropathy.[52,53] The inconsistency of these outcomes, the common side effect of gastrointestinal distress, and drug-drug interactions leave this medication among the least often used in this class.

Topical Lidocaine

The relatively recent demonstration of the efficacy of topically delivered lidocaine in the form of a patch has revitalized interest in the strategy of local Na^+ channel blockade with anesthetics. The lidocaine patch 5% appears to target the abnormal evoked and spontaneous activity in damaged peripheral afferents in the epidermis and dermis. Three published, double-blind, vehicle-controlled, randomized clinical trials support the efficacy of the lidocaine patch 5% in patients with PHN and in patients with diverse peripheral neuropathic pain syndromes, including PHN.[41,63,78]

The positive outcomes in PHN provided the basis for Food and Drug Administration (FDA) approval of the lidocaine patch 5% for the treatment of PHN, and consensus guidelines have recommended its use as a first-line agent given its excellent tolerability and safety.[30] Results of an open-label trial in patients with painful diabetic neuropathy raise the possibility that the lidocaine patch may be effective in neuropathic pain states even in the absence of allodynia; however, a blinded controlled study of this phenomenon would be necessary to confirm any benefit beyond the placebo effect.[6] In addition, the lidocaine patch has not been the subject of a blinded study in head-to-head comparison with orally active treatments so conclusions about its relative efficacy can only be based on indirect comparisons, with all of their potential problems. Unlike many other neuropathic treatments, there is no need for titration, and there are no significant systemic side effects or drug interactions when used at the recommended dose.[41,78]

Phenytoin

Phenytoin was one of the oldest neuroactive drugs to be reported as effective in the treatment of neuropathic pain on the basis of a study of patients with trigeminal neuralgia.[49] Inhibition of presynaptic glutamate release, in addition to Na^+ channel blockade, is thought to contribute to its mechanism of action.[107] There are several randomized clinical trials of phenytoin in other conditions.[103,108] The results of the 2 trials in peripheral diabetic neuropathy (300 mg/day) are contradictory.[15,85] A randomized, placebo-controlled trial in 20 patients receiving intravenous phenytoin proved more effective than placebo in reducing acute exacerbations of neuropathic symptoms.[62] Lack of statistical power to detect differences between placebo and phenytoin is one suggested explanation for the differences in results, but further studies have not been conducted. Use of phenytoin is limited due to multiple drug-drug interactions and complex kinetics.

Carbamazepine and Oxcarbazepine

Until the FDA approval of the lidocaine patch 5% for the management of PHN, carbamazepine was the only anticonvulsant approved by the FDA for the treatment of a neuropathic pain condition, specifically, trigeminal neuralgia. Similar to the local anesthetics, carbamazepine suppresses spontaneous activity in experimental neuromas.[12] There are clinical trials evaluating the efficacy of carbamazepine in neuropathic pain,[96] including double-blind, placebo-controlled, cross-over trials with positive results compared with placebo in patients with trigeminal neuralgia.[13,28,74,96]

Three randomized trials provide evidence of the effectiveness of carbamazepine in the treatment of diabetic neuropathy using a double-blind, cross-over design.[47,82,104] These trials have limitations, including inad-

equate washout periods, carryover effects, confounding interventions, and inadequate attention to the statistical analysis. The evidence for carbamazepine in the treatment of other neuropathic pain syndromes is considerably weaker, as exemplified by studies of PHN.[43] A recent, small study comparing gabapentin and carbamazepine in carpal tunnel syndrome demonstrated comparable efficacy.[35] Unfortunately, the apparent efficacy demonstrated in the trials of the 1960s[13,74,82] has not been further investigated in more recent and rigorously designed trials. Clinical use of carbamazepine is complicated by its collateral central nervous system side effect of sedation, drug interactions, and need for regular monitoring (hepatic and hematologic).

Oxcarbazepine is a 10-keto analogue of carbamazepine. There have been 3 double-blind, randomized clinical trials comparing oxcarbazepine and carbamazepine in patients with trigeminal neuralgia.[8] One study (n = 48) evaluated patients with newly diagnosed trigeminal neuralgia and two (n = 84) assessed those with refractory trigeminal neuralgia. In those newly diagnosed, the median daily dose was 750 mg/day for oxcarbazepine, whereas in those with refractory symptoms it was 1100 mg/day. There were no significant differences with regard to number of attacks per week, evoked pain, and global assessment of tolerability and efficacy between oxcarbazepine and carbamazepine. Rates of adverse effects of vertigo, fatigue, and somnolence were lower in the oxcarbazepine group. A recent, large, randomized, 4-month trial in patients with diabetic neuropathy demonstrated early and sustained pain reduction compared with placebo, but the results of additional pivotal trials in this condition have yet to be reported.[26] A trial of oxcarbazepine in painful lumbar radiculopathy has also recently been completed.[29]

Lamotrigine

Lamotrigine, a phenyltriazine derivative, is a newer antiepileptic agent initially approved as adjunctive therapy for complex partial seizures. Lamotrigine has multiple putative mechanisms of analgesic action. Lamotrigine blocks VGSCs.[55] Lamotrigine also decreases Ca^{2+}influx through suppression of VGCCs.[101] This activity has been demonstrated in neural tissue involved in seizure activity (eg, hippocampus) and not in regions integral to pain signaling such as the dorsal horn and dorsal root ganglion.[100] In an animal model of chronic hyperalgesia associated with streptozotocin-induced diabetes, lamotrogine demonstrated analgesic properties.[65]

There are multiple randomized trials of small-to-moderate size that show efficacy across a range of neuropathic pain states. Lamotrigine, typically at dosages above 200 mg daily, has demonstrated efficacy in reducing the pain associated with diabetic neuropathy, trigeminal neuralgia, HIV neuropathy, central neuropathic pain, and poststroke pain.[33,38,88,89,99,109] Patients with incomplete spinal cord injury experienced a mean reduction in overall pain intensity of 25%, with greatest reduction in brush evoked allodynia in regions of spontaneous pain.[38] These promising results are offset by high dropout rates due to the slow titration paced to minimize the incidence of rash.[88] In one double-blind, placebo-controlled study of 100 patients with neuropathic pain at dosages of 200 mg or less, there was no significant relief compared with placebo, but the presence of neuropathic symptoms rather than a etiologic diagnosis was the basis for including patients in this trial.[61] Most recently, two large multicenter trials in patients with diabetic neuropathy each failed to demonstrate pain reduction compared with placebo in intention-to-treat analyses of the primary endpoint of pain reduction, and a relatively high dropout rate may have reflected poorer tolerability at higher dosages (> 300 mg daily).[84] Therapeutic liabilities include relatively high incidence of rash and drug-drug interactions.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) were among the first class of medications proven effective for chronic neuropathic pain using a randomized, double-blind placebo-controlled research design.[102] Their efficacy has been repeatedly confirmed in multiple consecutive rigorously conducted randomized trials in patients with diabetic neuropathy and PHN.[59,90] There is some evidence that the pain relief and antidepressant effects are independent of one another.[60] The efficacy of these drugs has until recently been ascribed to noradrenergic and serotonergic reuptake inhibition. This activity occurs in supraspinal pathways and likely modulates pain through descending inhibitory pathways. Although amitriptyline blocks TTX-R channels, it is unclear to what extent VGSCs are involved in the efficacy of TCAs.[11,20]

The high rate of unpleasant anticholinergic side effects, most often dry mouth and constipation, limit treatment adherence in many patients. Comparable efficacy with agents from other classes is offset by the need to use TCAs very cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy, and with the increased risks of serious cardiac events at higher dosages.[64,71]

Ca^{2+}Channel Blockade

Ca^{2+} channels (VGCCs) modulate nociceptive transmission at the level of the neuronal synapse in the central nervous system. The role of the L, N, and P/Q type VGCCs varies with the nature of neural injury.[98] One indication of the important role played by these channels is the dense expression of the N-type channels in the superficial laminae (I, II) of the dorsal horn, the site of synapse for first-order primary afferent neurons. VGCCs are inactivated by large-amplitude depolarizations. With depolarization, there is an influx of Ca^{2+} ions into neurons and release of neurotransmitters such as GABA, glutamate, and norepinephrine. Perineural administration of Ca^{2+}channel blockers inactivates N-type Ca^{2+}channels. In animal models, this intervention reduces heat hyperalgesia and mechanical allodynia.[106] Intrathecal delivery of antagonists to VGCCs shows that blockade of N, P/Q,

and L type channels reduces pain, allodynia, and hyperalgesia.[98] Increased rates of depolarization at N-type VGCC in these neurons and the attendant neurotransmitter release would seem to facilitate the hyperexcitability of chronic neuropathic pain states.

A growing body of evidence points to a distinct pattern of Ca^{2+}channel subunit expression in animal models of chronic neuropathic pain.[18,67] Peripheral nerve injury models induce upregulation of the $\alpha_2\delta$ subunit and correlate with allodynic pain behavior.[67] Gabapentin reverses allodynic behavior in rats with neuropathic pain and suppresses peripheral ectopic afferent discharge at injured nerve sites.[69] The $\alpha_2\delta$ subunit expressed in the dorsal root ganglion cell differs from those throughout the brain and spinal cord.[25] Such a variation could account for the analgesic properties of gabapentin.

Gabapentin

The efficacy of gabapentin in reducing neuropathic pain behavior in animal models and the emerging body of clinical evidence supporting its use in patients with neuropathic pain has intensified research into the role of Ca^{2+}channels in the pathophysiology of neuropathic pain.[42,92] The extensive study of gabapentin in multiple, double-blind, placebo-controlled trials supports its use in the treatment of chronic neuropathic pain.[30] Pain states, including PHN, diabetic polyneuropathy, mixed neuropathic syndromes, Guillain-Barre syndrome, and acute and chronic spinal cord injury, have all been evaluated.[30] Two large multicenter, double-blind, placebo-controlled, randomized clinical trials demonstrated gabapentin at a target dosage of 3600 mg/day reduced pain from PHN and diabetic neuropathy.[5,79] Together these trials totaled more than 400 subjects, making their size far larger than any previous randomized controlled trials of drug therapy for neuropathic pain. The most common side effects in these trials were related to CNS depression and included dizziness, sedation/somnolence, and ataxia. Patients in the trial of gabapentin for diabetic neuropathy had a median age considerably lower than in the PHN trials but with the same overall frequency of side effects.[5]

The efficacy and tolerability of gabapentin was recently reproduced in a trial in PHN with target dosages of 1800 and 2400 mg and the reduction in average daily pain score was equivalent to that seen in earlier trials.[72] The lack of drug-drug interactions facilitates the use of combination regimens with gabapentin. A recent trial of patients with diabetic neuropathy and PHN demonstrated superior relief at lower doses of each drug when used in combination as compared with single-agent therapy.[46] In another recent trial, significant improvements were seen for the endpoints of burning pain and hyperalgesia at some follow-up visits but not for allodynia.[87] In several trials, improvements in sleep, mood, and other quality of life measures were also demonstrated.

Two comparative studies with gabapentin and amitriptyline in the treatment of painful diabetic neuropathy have been conducted, one an open-label study and one a randomized cross-over trial.[19,61] The randomized trial did not demonstrate a significant difference between amitriptyline and gabapentin at relatively low daily mean dosages of 59 mg and 1565 mg, respectively.[64] The most commonly encountered side effects of gabapentin include somnolence and dizziness. Dosage adjustment is required in patients with renal failure. Evidence of efficacy, ease of monitoring, low incidence of serious adverse events, and few drug interactions have contributed to the widespread use of gabapentin.

Pregabalin

Pregabalin, like gabapentin, interacts with the $\alpha 2\delta$ subunit of the voltage-gated Ca^{2+} channel. The decrease in Ca^{2+}influx reduces the presence of glutamate, substance P, and norepinephrine in the synapse.[27,95]

The efficacy of pregabalin (dosage range 150-600 mg daily) in the treatment of PHN and diabetic neuropathy has been shown in multiple large, multicenter, placebo-controlled trials.[31,56,76,83,73] In addition to significant reductions in pain intensity, pregabalin has demonstrated improvement in sleep and other aspects of physical and emotional functioning that are commonly disturbed in patients with chronic pain.[56,83] The percentages of patients obtaining a 50% reduction in pain intensity were comparable at 150 mg (26%) and 300 mg (28%) in patients with PHN.[83] The most common adverse effects in these trials were dizziness and somnolence. As with gabapentin, there appear to be relatively few ion channel effects outside of the central nervous system. The FDA has recently approved pregabalin for the treatment of PHN and painful diabetic neuropathy, which makes pregabalin the first treatment approved for the treatment of more than one chronic neuropathic pain condition.

Topiramate

Topiramate has multiple putative mechanisms of analgesic activity, including: modulation of voltage-gated Na channels, potentiation of GABAa inhibition, blockade of VGCCs, and antagonism of the kainate subtype of glutamate receptor, which has been shown to reduce pain evoked by facial movement after oral surgery.[44,86] A small (n = 27) double-blind placebo-controlled trial showed 400 mg/day superior to placebo for painful diabetic neuropathy, but only 1 of 4 large trials demonstrated superior pain relief in diabetic neuropathy compared with placebo.[32,70,97] In this trial, topiramate was titrated to 400 mg daily as tolerated and not only reduced pain more effectively than placebo but was also associated with significant reductions in body weight without the disruption of glycemic control.[70]

Although the benefit in diabetic neuropathy is equivocal, results in small trials of patients with trigeminal neuralgia have generally had favorable results.[45,110] Topiramate tends to have a higher rate of psychomotor slowing, carbonic anhydrase inhibition, renal stones, and drug-drug interactions than other anticonvulsant drugs.

Levetiracetam

Levetiracetam, an antiepileptic agent recently approved for adjunctive epilepsy therapy, selectively inhibits its N-type VGCCs.[57,66] This mechanism may account for the reduction in pain behavior in neuropathic animal models.[1] A small (n = 10), open-label trial of patients with PHN refractory to first-line treatments was encouraging with regard to tolerability (mean daily dose 2200 mg/day) as well as analgesic effects, but placebo-controlled trials are required to evaluate the efficacy of levetiracetam in patients with neuropathic pain.[81]

Ziconotide

Ziconotide is a selective N-type voltage-sensitive Ca^{2+}channel blocking agent that has recently been approved by the FDA for the management of severe chronic pain in patients for whom intrathecal therapy is warranted and who are intolerant of or refractory to other treatment—eg, systemic analgesics, adjunctive therapies, and intrathecal morphine. In animal models, intrathecal administration optimizes the antinociceptive effects and reduces associated decreases in sympathetic tone.[9] A recent trial of intrathecal ziconotide in patients with refractory pain associated with cancer or AIDS showed significant reduction in pain.[91] There was little evidence of declining benefit suggestive of drug tolerance in the maintenance phase. Central nervous system side effects, which appear to be related to N-type channel blockade in the granular cell layer of the cerebellum, are reduced with a decreased infusion rate and remit following infusion. A synthetic, small-molecule equivalent of ω-conopeptide is not yet available in the form of an oral medication.

Conclusions

Advances of the last decade have transformed the 75-year-old therapeutic strategy of ion channel blockade for the treatment of neuropathic pain. Local modes of drug delivery, novel Ca^{2+}channel interactions among newer agents, and previously unrecognized Na^{+}channel mechanisms of traditional, first-line medications represent important new developments. These strides are driving the drug discovery process in the direction of ion channel therapeutics. Improved tolerability and reduced drug-drug interactions have accelerated the adoption of topical lidocaine and gabapentin among nonspecialist clinicians treating pain. Still, there is an unmet need for the treatment of neuropathic pain states because the relief afforded by these medications is partial and response is generally reported in no more than 40% to 60% of treated patients. In addition, the prevalence of neuropathic pain states continues to rise with an aging population, and there is a large cohort of patients who are unable to tolerate or do not respond to existing medications. Treatment decisions about combination analgesic regimens will be increasingly informed by a better understanding of specific ion channel activity. As the molecular characterization of the analgesic properties of medications grows more precise, so will the importance of mechanism-based approaches to treatment. Developing and disseminating the clinical tools to identify the neural mechanisms responsible for pain in an individual patient are essential to advancing beyond the traditional disease-based treatment paradigm.

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