Targeting Voltage-Gated Calcium Channels for Neuropathic Pain Management

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Summary: Voltage-gated calcium channels (VGCC) play obligatory roles in diverse physiological functions. Pathological conditions leading to changes in their biophysical properties and expression levels may cause malfunctions of VGCC-mediated activities, resulting in disease states. It is believed that changes in VGCC properties under pain-inducing conditions may play a causal role in the development of chronic pain, including nerve injury-induced pain or neuropathic pain. For the past several decades, preclinical and clinical research in developing VGCC blockers or modulators for chronic pain management has been fruitful, leading to some U.S. Food and Drug Administration-approved drugs currently available for chronic pain management. However, their efficacy in pain relief is limited in some patients, and their long-term use is limited by their side-effect profiles. Certainly, there is room for improvement in developing more subtype-specific VGCC blockers or modulators for chronic pain conditions. In this review, we summarized the most recent preclinical and clinical studies related to chronic pain medications acting on the VGCC. We also included clinical trials aiming to expand the application of approved VGCC drugs to different pain states derived from various pathological conditions, as well as drug combination therapies trying to improve the efficacies and side-effect profiles of current pain medications. **Key Words:** Chronic, neuropathic pain, voltage-gated calcium channels, analgesics.

INTRODUCTION

A recent survey has indicated that at least 50 million people in the United States suffer from chronic pain.[1] It is predicted that this number will increase dramatically due to advances in health care that will continue to prolong the lifespan of patients. In addition to adversely affecting quality of life, inadequate management of chronic pain also has profound social, economical, and psychological consequences. Current pain medications, both opioid and nonopioid, at best, cause partial pain relief in some, but not all, patients. In addition, long-term usage of these medications is often associated with intolerable side effects, some of which can be life-threatening. Therefore, there is an urgent need for safer and more specific analgesic medications for chronic pain management.

Even though different etiologies of chronic pain may have similar clinical manifestations, chronic pain can derive from different pathological conditions that each mediate chronic pain states by unique mechanisms. Thus, directing our treatment toward a limited number of targets by medications in our current toolbox could render partial pain relief in some patients only. Combinational treatment is an option to improve efficacy and reduce side effects. Unfortunately, most of the currently available analgesic medications act through targets that are not only important in pain processing, but also critical in mediating normal physiological functions, which therefore lead to intolerable side effects, especially after long-term usage. Individualized pain management based on pain-inducing pathological conditions would have the least interference with normal physiological functions, and is therefore an ideal approach in chronic pain management.

Voltage-gated calcium channels (VGCC) or their subunits are considered one family of molecules with therapeutic potentials in chronic pain management. The VGCC are assembled through interactions of different subunits,[2] namely $\alpha 1$ ($Ca_V\alpha 1$), β ($Ca_V\beta$) $\alpha_2\delta$ ($Ca_V\alpha_2\delta$) and γ ($Ca_V\gamma$). So far, 10 channel-forming $Ca_V\alpha$ subunits, encoded by distinct genes, have been identified.[2]

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These $Ca_V\alpha$ subunits consist of four homologous transmembrane regions, and each is composed of six transmembrane domains linked by intracellular loops and amino and carboxy termini. The diversified physiological and pharmacological properties of VGCC are mainly derived from the existence of these $Ca_V\alpha$ subunits. Four $Ca_V\beta$ subunits have been identified so far. They all have alternative splicing variants.[3] The $Ca_V\beta$ subunits are entirely intracellular, phosphorylated by multiple protein kinases, including protein kinase C and cAMP-dependent protein kinase, and they play a critical role in cell surface expression and modulating the gating properties of the $Ca_V\alpha$ subunit.[4] Four distinctive $Ca_V\alpha2\delta$ genes, $Ca_v\alpha_2\delta_1$, $Ca_v\alpha_2\delta_2$, $Ca_v\alpha_2\delta_3$, and $Ca_v\alpha_2\delta_4$ have been identified.[5,6] Their products and splice variants have specific tissue distribution patterns.[6–9] The $Ca_V\alpha2\delta$ subunit consists of two disulfide-linked peptides (α_2 and δ) that are encoded by the same gene.[10,11] It is highly glycosylated and mainly extracellular, with a single transmembrane domain and five intracellular carboxyl terminal amino acids.[12-14] Data from in vitro studies have shown that co-expression of $Ca_V\alpha2\delta$ with other calcium channel subunits increases and stabilizes current amplitude,[13,15-20] channel binding sites, and binding affinity for N-type VGCC ligands.[19,21] Three-dimensional structural analysis of the L-type VGCC by electron cryo-microscopy has indicated that the extracellular $Ca_V\alpha_2$ subunit protrudes from the membrane in close proximity to the channel forming $Ca_V\alpha$ subunit.[22] Recent findings have indicated that the $Ca_V\alpha2\delta$ subunit is also involved in cellular trafficking of the calcium channel complex.[23,24] These findings suggest that the $Ca_V\alpha2\delta$ subunit is likely involved in VGCC assembly and stabilization, modulation of $Ca_V\alpha$ subunit functions, and ligand binding. The $Ca_V\gamma1$ subunit is a structural component for the skeletal muscle L-type calcium channels.[25–27] Whether other identified $Ca_V\gamma$ or $Ca_V\gamma$-like subunits associate with other types of VGCC remained to be confirmed.[28–32] The functional role of the $Ca_V\gamma$ subunit is not well understood.

Based on their physiological and pharmacological properties, VGCC can be subdivided into low voltage-activated T-type ($Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$), and high voltage-activated L- ($Ca_v1.1$ through $Ca_v1.4$), N-($Ca_v2.2$), P/Q-($Ca_v2.1$), and R-($Ca_v2.3$) types, depending on the channel-forming $Ca_V\alpha$ subunits.[2,33] All of these five subclasses of calcium channels are found in the central and peripheral nervous systems.[33] Regulation of intracellular calcium through activation of these VGCC plays obligatory roles in: 1) neurotransmitter release, 2) membrane depolarization and hyperpolarization, 3) enzyme activation and inactivation, and 4) gene regulation.[34–40] A large body of data has clearly indicated that VGCC are implicated in mediating various disease states,[38,41] including pain processing.[40,42–45] This review focuses on recent preclinical and clinical studies regarding VGCC as targets for chronic pain management, especially neuropathic pain management. For more generalized reviews about the biophysical properties, and plasticity of VGCC on other disease states, the readers are referred to other recent reviews.[46,47]

CALCIUM CHANNEL DRUGS FOR PAIN MANAGEMENT

The diversities in biophysical properties and tissue-specific expression of VGCC thus become an important issue in drug specificity and safety in developing analgesic drugs for pain management. Data from preclinical studies have indicated that most neurons, including sensory neurons[48] and spinal dorsal horn neurons,[49–51] express multiple types of VGCC. Several types of VGCC are considered potential targets for analgesics based on their distribution, biophysical/pathological roles, and plasticity under pain-inducing conditions.[52] We aim here to highlight both preclinical and clinical advances in VGCC drug use, including combinational therapies, in pain medicine. A summary of the current VGCC medications that are commonly used for pain management is available in Table 1. The U.S. Food and Drug Administration (FDA)-approved indications for each are noted. A summary of ongoing clinical trials, as listed on clinicaltrials.gov, is available in Table 2, which provides the reader with information regarding studies using these common VGCC drugs to treat non-FDA-approved pain etiologies and indications.

N-type VGCC blockers

N-type VGCC are highly expressed in dorsal root ganglion (DRG) cell bodies and at the presynaptic terminals where afferent sensory fibers form synapses with postsynaptic dorsal horn neurons,[47,53–55] implying an important role of these calcium channels in mediating normal sensory neuron excitability and neurotransmitter release. Changes in the biophysical properties and enhanced expression of these VGCC under pain-inducing pathological conditions would likely enhance synaptic vesicle release of pain-inducing transmitters, such as glutamate, substance P, and calcitonin gene-related peptide on stimulation that could activate interneurons and projection neurons, altering sensory excitability and leading to pain sensations. In addition, N-type VGCC are unique in that they are a target for descending activation of adrenergic pathways by norepinephrine[56] and for inhibition by opioid pathways.[57,58] A role for N-type VGCC in neuropathic pain is solidified by findings indicating that spinally delivered N-type calcium channel antagonist can block nerve injury-induced tactile allodynia,[59] and dorsal horn neuronal responses.[50] Evidently, blocking the N-type VGCC at the levels of spinal cord and sensory neurons results in inhibition of stimulus-evoked release of pain-inducing peptides, such as substance P, calcito-

Table 1. *Summary of Current Calcium-Channel Drugs in Common Clinical Use for Pain Management*

Drug	FDA Indications	Adverse Reactions	Reference
Gabapentin	2002: Postherpetic neuralgia; 1994: epilepsy (partial seizures), pediatric partial seizures	Dizziness, somnolence, peripheral edema, nausea, dyspepsia, increased appetite, constipation	http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020235s041,020882s028,021129s027lbl.pdf
Pregabalin	2004: Neuropathic pain associated with diabetic peripheral neuropathy; postherpetic neuralgia; adjunctive therapy for adult patients with partial onset seizures; fibromyalgia	Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, abnormal thinking (difficulty with concentration/attention)	http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021446s013s014lbl.pdf
Ziconotide	2004: Management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine	Vertigo, vision blurred, asthenia, abnormal gait, pyrexia, rigors, sinusitis, anorexia, muscle spasms, pain in limb, amnesia, ataxia, dizziness, dysarthria, dysgeusia, headache, memory impairment, nausea, nystagmus, somnolence, tremor, anxiety, confusion, insomnia, urinary retention, pruritus, increased sweating	http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021060s003lbl.pdf

FDA = U.S. Food and Drug Administration; IT = intrathecal.

nin gene-related peptide, and excitatory neurotransmitter, glutamate.[43,60–62] Nerve or tissue injury-induced tactile allodynia and thermal hyperalgesia, but not acute pain states, are suppressed in mice lacking the N-type calcium channel-forming $Ca_V\alpha$ subunit.[63–65] This implies that the N-type VGCC are more directly involved in chronic, rather than acute, nociception. This is consistent with data from direct blockade of N-type VGCC by cone snail peptides ω-conotonix-GVIA and ω-conotonix-MVIIA (ziconotide or Prialt) that leads to inhibition of neuropathic and inflammatory pain, but not acute pain, in animal models.[52] Interestingly, splicing variants of the N-type VGCC have been identified in sensory neurons.[66–68] With validation of their functional contribution to pain processing, these subtypes of N-type VGCC could be potential targets for specific analgesic drugs.

Peptide N-type VGCC blockers

The FDA approval of ziconotide, or the synthetic version of ω-conotonix-MVIIA (also called SNX-111, or Prialt (Elan Pharmaceuticals, Inc., San Diego, CA), for the treatment of chronic severe pain refractory to other current pain medications in December 2004 in the United States and in Europe[69] (Table 1) marked the first clinical application of N-type VGCC peptide blockers in chronic pain management. ω-conotonix-MVIIA is a 25-amino acid peptide isolated from the marine fish-hunting cone snail, *Conus magus*.[70] Due to the peptidergic nature of this drug, it is only approved for intrathecal application. Ziconotide can block N-type VGCC currents with high potency, but in a reversible manner.[71,72] Data from preclinical studies have indicated that blocking N-type VGCC by this toxin leads to diminished neurotransmitter release in the spinal cord,[73] and diminished postoperative, inflammatory, and neuropathic pain states in animal models.[59,74–76] The analgesic effect of intrathecal ziconotide is more potent and longer lasting than intrathecal morphine without tolerance or cross-tolerance to morphine analgesia.[74,75]

Clinical trials of intrathecal application of this peptide drug result in significant pain relief for patients with severe chronic pain (Table 2), including neuropathic pain and pain secondary to cancer or AIDS. Several reviews summarizing the details of some early clinical trials were recently published.[77–79] Briefly, the first randomized, double-blind, placebo-controlled pilot study for pain relief with intrathecal ziconotide was in patients undergoing surgery.[80] Patients received either a placebo or one of two intrathecal ziconotide doses (0.7 μg/h and 7.0 μg/h) postoperatively during the following 48 h. The mean daily morphine consumption from patient-controlled administration in the 24- to 48-h period was significantly lower in patients receiving ziconotide than in placebo-controlled patients. Pain scores in both ziconotide groups were lower than in the placebo group. Adverse events were more frequent on the higher ziconotide dose. In an open-label clinical study,[81] 31 male patients with chronic pain who had failed opioid management received continuous intrathecal ziconotide infusions. The average pain reduction was 43% in 19 out of 24 patients who completed the study. The concomitant use of opioids was reduced by at least 50% in 15 patients. Two multicenter, randomized, double-blind, placebo-controlled trials in

Table 2. *Summary of Clinical Trials by Pain Etiology**

Study Drug	Study Indication
Ziconotide, nimodipine, pregabalin	AIDS/HIV
Pregabalin	Anxiety, preoperative
Ziconotide, gabapentin, lamotrigine, pregabalin	Cancer
Amlodopine, gabapentin, ziconotide, nifedipine, pregabalin, eperisone	Chronic pain syndromes (pelvic, chronic prostatitis, abdominal, chronic pain secondary to trauma, chronic low back pain, chronic pancreatitis, vulvodynia)
Verapamil	Cluster headache
Pregabalin	Complex regional pain syndrome
Pregabalin	Essential tremor
Lamotrigine, pregabalin	Facial pain (excluding postherpetic neuralgia)
Gabapentin, pregabalin	Fibromyalgia
Diltiazem	Hemorrhoidectomy
Gabapentin, pregabalin	Multiple sclerosis
Gabapentin, gabapentin XR, pregabalin, lamotrigine	Peripheral neuropathy (chemotherapy, radiation, alcohol, diabetic, vascular, idiopathic)
Gabapentin	Phantom limb pain
Gabapentin, gabapentin XR, lamotrigine, pregabalin	Postherpetic neuralgia
Gabapentin, pregabalin	Postoperative pain (sternotomy, thoracotomy, hip surgery, joint replacement, cesarean section, tonsillectomy, keratectomy, inguinal hernia repair, spinal fusion, knee arthroscopy, scoliosis surgery, CABG, hysterectomy, cholecystectomy, mastectomy, axillary node dissection, bunionectomy)
Pregabalin	Post-traumatic pain
Pregabalin	Radiculopathy
Pregabalin	Spinal cord injury
Pregabalin	Spinal stenosis
Pregabalin	Stroke
Gabapentin	Stump pain
Gabapentin	Tinnitus
Lamotrigine	Trigeminal neuralgia

*Source: clinicaltrials.gov.

patients with chronic cancer or AIDS-associated pain ("malignant pain")[82] or with nonmalignant pain[83] were conducted. In the "malignant," chronic cancer/AIDS-related pain trial,[82] ziconotide improved the mean visual analog scale of pain intensity (VASPI) scores by 53%. In addition, 53% patients in the ziconotide group had pain relief classified as moderate to complete compared with 18% patients in the placebo group. Five patients in the ziconotide group had achieved "complete" pain relief. In the "nonmalignant" pain trial,[83] 240 patients were randomized to ziconotide versus a placebo. Ziconotide reduced the mean VASPI scores by 31% (compared with 6% for the placebo group). In addition, more than 43% of patients in the ziconotide group had moderate-to-complete analgesia, compared with 17% in the placebo group.

Several additional studies published in 2006 assessed the ideal effective dose and tolerability of ziconotide. In three well-designed trials with up to 21-day durations,[84] titration of ziconotide resulted in significant improvement in the VASPI scores for chronic malignant or nonmalignant pain compared with a placebo. The analgesic effects of ziconotide remained for up to 12 months in long-term, open-label trials. In addition, lower incidence and severity of adverse effects were observed in patients with low initial doses and gradual titration to achieve analgesia. In a randomized, double-blind, placebo-controlled study,[85] slower titration of intrathecal ziconotide to a lower maximum dose was associated with a significant improvement in pain relief and was better tolerated compared with faster titrations and higher maximum mean dose reported in two earlier placebo-controlled trials. It was suggested that administration of intrathecal ziconotide at a low starting (maximum) dose of 0.5 μg/day and a limitation of dose escalations to no more than 0.5 μg/day may limit adverse effects.[86]

A recent case report highlighted the use of ziconotide in a patient with recalcitrant pain post-spinal cord injury, with both at-level and below-the-neurological-level of neuropathic pain syndromes. When intrathecal hydromorphone was used as a treatment modality, the patient's at-level, but not the below-level, pain was reduced. Conversely, when intrathecal ziconotide was administered, analgesia was positive for the below-level, but only minimally for the at-level, pain. When combination therapy with intrathecal hydromorphone and ziconotide was used, analgesia was sufficient for both pain components. This study implies that central pain due to spinal cord

injury may be an indication for intrathecal ziconotide, particularly in combination with intrathecal opioids.[87]

The usage of this peptide drug is limited by the route of administration and undesirable side effects, including sedation, dizziness, nausea, emesis, somnolence, headache, confusion, memory impairment, slurred speech, nystagmus, double or blurry vision, urinary retention, hypotension, elevated creatine kinase levels, and gait abnormality.[78,88–90] It is believed that the serious side effects of ziconotide are derived from complete blockade of the N-type VGCC that would affect the normal biophysical functions of widely distributed N-type VGCC.[91] However, it is argued that more convincing data are needed to make definitive conclusions because similar adverse effects are not detectable in N-type VGCC knockout mice, which have no detectable evidence of developmental compensation from other types of VGCC.[89] It is possible that some of these adverse effects may be secondary to effects at other receptors besides the N-type VGCC. Most adverse events occur during the first week of treatment. After 6 months of treatment, the incidence of adverse events is noted to be 0 to 35% of that reported in the first month of treatment.[84] Potential contamination of intrathecal pump devices used to administer ziconotide (or any other intrathecal agent) may increase the risk of meningitis.[77] The neurological side effects of ziconotide dictate that the drug should be used with caution and careful dose titration. Particular symptoms may correlate with the rate of infusion.[90] Because addiction and tolerance are not detectable with the analgesic effects of ziconotide,[88] but are often observed with the use of opioid analgesics, intrathecal ziconotide could be an option for replacing intrathecal morphine for chronic severe pain relief. However, the combination of opioid withdrawal symptoms and the cognitive/psychiatric adverse effects of ziconotide could make the conversion challenging. Successful treatment with ziconotide monotherapy has been suggested to include physician and psychological supports to decrease possible adverse psychological and physiological complications.[92]

Overall, although pain relief by ziconotide is accompanied with some adverse effects, use of this analgesic has several benefits. Ziconotide is less mood-altering than morphine for comparable analgesia and has the advantage of lacking addiction, opioid-induced hyperalgesia, and other systematic effects commonly observed with opioids.[93] For these reasons, the Polyanalgesic Consensus Conference of 2007 puts ziconotide in the first line of intrathecal therapy management, along with morphine and hydromorphone, in its recommended algorithm for nociceptive, mixed, and neuropathic pain.[94] As summarized in a recent review, the evidence for short-term improvement of malignancy-related pain or neuropathic pain with intrathecal ziconotide is also strong.[95]

Nevertheless, searching for safer analgesic peptide antagonists against the N-type VGCC continues. It has been reported that ω-conotonix-GVIA, a 27-amino acid peptide isolated from the cone snail, *Conus geographus*, also exhibits analgesic properties in animal models.[52] In contrast to ziconotide, ω-conotonix-GVIA is an irreversible inhibitor of N-type VGCC,[96] which precludes its clinical application due to potential severe side effects. However, recent studies have indicated that binding of this toxin peptide to the N-type VGCC can also modulate (inhibit) N-type VGCC gating properties so that approximately 50%, instead of a complete blockade, of the calcium influx during an action potential is inhibited,[91] in addition to the primary pore blocking mechanism. This would provide a means to normalize elevated (activated) N-type VGCC activities in a disease condition, such as chronic pain, but preserve the biophysical functions of N-type VGCC in maintaining normal physiological functions, and thus reduce adverse side effects. High-throughput screening using a scintillation proximity assay has been used to search for small molecules that can displace ω-conotonix-GVIA binding to the N-type VGCC in an attempt to find N-type VGCC modulators with high affinity to the ω-conotonix-GVIA binding sites on the N-type VGCC.[97]

Another 27-amino acid peptide ω-conotonix-CVID, also called AM336, from the cone snail, *Conus catus*, is perhaps the most selective of all N-type VGCC peptide blockers with greater than 24 hours of analgesia observed in rats from subnanomolar intrathecal doses.[73,98,99] Intrathecal administration of this peptide drug into rat pain models results in inhibition of spinal release of pain-inducing peptides and potent dose-dependent anti-nociception.[73,98] In addition, AM336 showed a greater ratio of analgesic efficacy to behavioral toxicity than ziconotide,[73,98] probably due to its greater selectivity for N-type in comparison with P/Q type VGCC.[71] This peptide drug was assessed in a phase I clinical trial in oncology patients with severe pain[100] and its efficacy was established in a small phase IIa clinical trial for patients with severe cancer pain.[40] Unfortunately, the side effects were undesirable and dose limiting. The adverse effect profile is surprising given the 10^6-fold binding selectivity of this peptide for N-type in comparison with P/Q-type VGCC,[71] and it may be secondary to supraspinal effects.

Small molecule N-type VGCC blockers

The potency of ziconotide in chronic pain relief, and its association with an undesirable administration route and an undesirable side-effect profile, has prompted a race in searching for small molecules that would be orally active and have an acceptable therapeutic window for chronic pain management. Using a high-throughput fluorescence-based in vitro assay to compare IC_{50} values of blocking both N-type and L-type VGCC in a human

neuroblastoma cell line for identifying specific N-type VGCC blockers from its corporate compound library, scientists in Ionix Pharmaceuticals Ltd. have developed a series of new N-type VGCC blockers derived from structural modifications of "hit" structures.[101] After structural and activity relationship analysis, compounds with up to 30-fold of N-type/L-type VGCC selectivity and up to 0.2 μM in IC_{50} values are identified. Unfortunately, analgesic efficacies in chronic pain models were not included in the study. Further investigations for the analgesic efficacy and toxicity in animal pain models may prove the usefulness of these compounds for further development as therapeutic agents for chronic pain management.

Indirect inhibitors of N-type channels

N-type VGCC can be modulated by morphine, an important analgesic. Binding of morphine to μ-opioid receptors activates $G_{\beta\gamma}$ which translocates to the membrane and binds to the N-type VGCC. A massive G-protein-dependent inhibition of calcium currents results in an inhibition of neurotransmitter release,[2,45,102] and reduces the ability of the DRG sensory neurons to propagate pain signals. This process is at least partially responsible for morphine's analgesic effect, but can also contribute to tolerance development. Combination of ziconotide with μ-opioids shows synergistic analgesia when administered intrathecally.[74,98,103] This combination therapy may help to reduce opioid tolerance, a poor side-effect profile, and the potential for opioid-induced hyperalgesia, all of which limit the long-term usefulness of μ-opioid receptor agonists in pain medicine. Spinal noradrenaline can reduce VGCC-mediated transmission by presynaptic and postsynaptic inhibition, and by α1-adrenoceptor-mediated activation of inhibitory interneurons.[40] These may explain the effectiveness of α2-adrenergic agonists (such as clonidine) and nonselective small molecule norepinephrine transporter (NET) inhibitors (such as duloxetine) in pain relief. However, these medications also have limiting side-effect profiles.[104] Highly selective NET inhibitors, χ-conopeptides, have been isolated from the cone snail, *Conus marmoreus*.[105] It was demonstrated that the χ-conopeptide NET-binding site partially overlaps the tricyclic antidepressant NET-binding site.[106] Based on studies in rat neuropathic pain models, the χ-conopeptide compound MrIA (Xen2174) was found to produce strong anti-allodynic effects without significant side effects after intrathecal administration.[107] A phase I/IIa clinical trial involving intrathecal evaluation of Xen2174 in cancer patients with intractable pain shows initial promising results.[40] This line of compounds may represent an important option in the search to identify a potentially different therapeutic approach in targeting VGCC for chronic pain management.

Peptide T-type VGCC blockers

Low-voltage T-type VGCC are found in DRG primary afferent cell bodies and in free nerve endings. They contribute to the initiation of the action potential in these locations by lowering the required threshold for activation.[108] By promoting burst activity and synaptic excitation, enhanced T-type VGCC activity favors the development of pain.[51,109] T-type VGCC density has been increased in rat neuropathic pain models of diabetic neuropathy and chronic constriction nerve injury.[110,111] The facts that T-type VGCC knockout animals have hyposensitivity to pain and that intrathecal injection with T-type VGCC blockers or antisense oligonucleotides results in reduced excitability of the primary afferents and therefore reduced nociceptive responses all attest to their established role in the processing of pain, especially neuropathic pain.[51,112–118] However, the exact mechanisms underlying the role of T-type VGCC in nociception still remain elusive. Several regulatory mechanisms of T-type VGCC in pain processing have been proposed. These include redox modulation of T-type VGCC in rat peripheral nociceptors,[119] and the selective enhancement of T-type VGCC in nociceptive DRG neurons by reducing agents, such as L-cysteine, synthetic, and endogenous chelators of zinc.[119] The latter is supported by the findings that peripherally injected reducing agents produce thermal hyperalgesia in wild-type but not Cav3.2 knockout mice, indicating that T-type VGCC may have a special role in peripheral sensitization.[119] Currently, ethosuximide is the only T-type VGCC blocker approved for human use.[120]

L-type VGCC blockers

Evidence from recent clinical studies shows that L-type VGCC blockers, such as topiramate, are efficacious for neuropathic pain management, and leads to the suggestion that this medication should be a third-line agent for neuropathic pain treatment.[121] In one study, topiramate has been shown to cause statistically significant reduction in pain intensity compared to a placebo, as measured on a 100-mm visual analog scale, for up to 12 weeks in diabetic peripheral neuropathy patients.[122] However, three other randomized, double-blind, placebo-controlled trials with more than 1,200 diabetic neuropathy patients failed to show statistically significant reductions in pain intensity after 18 to 22 weeks of treatment. In addition, these three studies also resulted in topiramate drop out rates ranging from 16% to 31% compared with 8% for a placebo. The most commonly reported adverse events were fatigue, paresthesias, nausea, somnolence, and diminished appetite.[123] Another study evaluated the efficacy of topiramate for pain in patients associated with chronic lumbar radiculopathy and found modest pain relief in the topiramate-treated group, but with a 24% drop out rate.[124] At least one

recent case report has suggested that topiramate may be a useful pharmacologic modality for pain relief in patients with postherpetic neuralgia who have failed other agents.[125] It has been reported that topiramate has other pharmacologic actions including blockage of voltage-gated sodium channels in a dose-dependent manner,[125] potentiation of GABA inhibition, and AMPA receptor blockade,[122–124,126] which may contribute to both its analgesic potential and its adverse side effects.

Other types of VGCC blockers

Contribution of other types of VGCC to pain processing have been suggested in some preclinical studies. Missense mutations in the $Ca_v2.1$ P/Q-type calcium channels lead to familial hemiplegic migraine, an inherited form of migraine with aura and hemiparesis.[127–129] In addition, R-type VGCC have been implicated in the processing of neuropathic pain and other pain states.[130] However, few clinical researches evaluating the efficacies of specific blockers to these VGCC in pain relief are available; thus, these are not covered in this review.

CALCIUM CHANNEL α2δ1 LIGANDS FOR PAIN MANAGEMENT

The unique features of the $Ca_v\alpha_2\delta$ subunit and a large body of recent findings have suggested that the $Ca_v\alpha_2\delta_1$ subunit may play an important role in neuropathic pain development. Biochemical data have indicated a significant $Ca_v\alpha_2\delta_1$, but not $Ca_v\alpha_2\delta_2$, subunit upregulation in the spinal dorsal horn, and DRG after nerve injury[23,131–135] that correlates with neuropathic pain development.[131,132,136] In addition, blocking axonal transport of injury-induced DRG $Ca_v\alpha_2\delta_1$ subunit to the central presynaptic terminals diminishes tactile allodynia in nerve injured animals, suggesting that elevated DRG $Ca_v\alpha_2\delta_1$ subunit contributes to neuropathic allodynia, even though a postsynaptic mechanism can not be completely ruled out.[23,24,136] Interestingly, the $Ca_v\alpha_2\delta_1$ subunit (and the $Ca_v\alpha_2\delta_2$, but not $Ca_v\alpha_2\delta_3$ and $Ca_v\alpha_2\delta_4$, subunits) is the binding site for gabapentin,[6,7,137] which has anti-allodynic/hyperalgesic properties in patients and animal models with unknown mechanisms.[131,132,138–143] Because injury-induced $Ca_v\alpha_2\delta_1$ expression correlates with neuropathic pain development and maintenance, and various calcium channels are known to contribute to spinal synaptic neurotransmission[50,144–149] and DRG neuron excitability,[66,149–151] injury-induced $Ca_v\alpha_2\delta_1$ subunit upregulation may contribute to the initiation and maintenance of neuropathic pain by altering the properties and/or distribution of VGCC in the subpopulation of DRG neurons and their central terminals, therefore modulating excitability and/or synaptic neuroplasticity in the dorsal horn. This is supported by findings from preclinical studies indicating that intrathecal antisense oligonucleotides against the $Ca_v\alpha_2\delta_1$ subunit can block nerve injury-induced $Ca_v\alpha_2\delta_1$ upregulation and prevent the onset of allodynia[152] and reserve established allodynia.[136]

Both gabapentin and pregabalin are structural derivatives of the inhibitory neurotransmitter GABA although they do not bind to $GABA_A$, $GABA_B$, or benzodiazepine receptors, or alter GABA regulation in animal brain preparations.[153] Binding of gabapentin and pregabalin to the $Ca_v\alpha_2\delta_1$ subunit of VGCC results in a reduction in the calcium-dependent release of multiple neurotransmitters,[121,154] leading to efficacy and tolerability for neuropathic pain management.[121]

Gabapentin

Gabapentin is approved by the FDA for postherpetic neuralgia, neuropathic pain, and partial seizures[155–157] (Table 1). Several studies also suggest a clinical role for restless leg syndrome,[158] general anxiety,[159] and general neuropathic pain.[141] In common practice, gabapentin is used as a first-line agent to treat neuropathic pain from central origin (such as stroke or spinal cord injury) or from peripheral origin (such as peripheral neuropathy or radiculopathy). Despite its role and ubiquity, several controlled trials demonstrate a low responder rate of approximately 32%.[155]

Gabapentin has inherent pharmacokinetic limitations; the half-life of gabapentin is short, and therefore administration must be frequent. In addition, gabapentin is absorbed actively via absorption pumps located in the upper gastrointestinal tract. Therefore, conventional sustained-release formulations, where drug release is prolonged and occurs throughout the gastrointestinal tract, would simply decrease the bioavailability of the drug.[160] Therapeutic doses and responses vary among patients and prediction of the ultimate desired doses is exceedingly difficult. Furthermore, most gabapentin absorption is nonlinear (i.e., as the dose is increased, the bioavailability decreases).[160–162]

The FDA has approved gabapentin at a dose of up to 1,800 mg/day. This drug is frequently used off-label for the treatment of other neuropathic pain conditions, including painful diabetic peripheral neuropathy and radiculopathy, at higher doses up to 3,600 mg/day.[141,163,164] It has been suggested that gabapentin may be effective for the treatment of chronic pain of any etiology, including musculoskeletal headache, cervical pain, neuropathic pain, lumbar pain, or multiple pains, such as fibromyalgia[165,166] (Table 2). Although gabapentin is well tolerated in studies, a statistically significant incidence of sedation, lightheadedness, and dizziness is noted when compared to control patients.[166]

Combinational treatment of gabapentin with other pain medications for pain management has been tested in numerous clinical trials. Combination treatment of gabapentin and morphine in an animal model of neuropathic

pain results in a significant increase in the inhibitory effect of morphine on the dorsal horn neural response to peripheral stimulation,[167] providing preclinical evidences to support that combination therapies with gabapentin may have clinical benefits in chronic pain management. A crossover study involving 57 patients with neuropathic pain demonstrated improved clinical outcomes when patients received a combination of morphine and gabapentin versus monotherapy.[168] A larger study with 338 patients demonstrated that co-administration of gabapentin and prolonged-release of oxycodone has a clinically meaningful effect in patients with painful (diabetic) neuropathy.[169]

Gabapentin extended-release

A gabapentin extended-release (ER) has been developed. Gabapentin ER was constructed using polymer-based AcuForm technology (Depomed, Inc., Menlo Park, CA). When taken with a meal, the tablet is retained in the stomach for up to 8 h and the drug is gradually released over 10 h to the small intestine, its optimal site of absorption.[162,170] This prolonged release was designed to provide similar or improved systemic exposure as compared with the immediate release formulation.

In an exploratory study, the daily exposure provided by less frequent gabapentin extended-release dosing (once- and twice-daily) was found not to be statistically different from that provided by gabapentin immediate-release, administered more frequently (three times a day [TID]). Gabapentin ER once-daily dosing was found to produce higher maximum plasma concentrations compared with the TID gabapentin immediate-release regimen and twice-daily gabapentin ER dosing was found to result in less fluctuation in plasma concentrations.[171]

A recent randomized, double-blinded, placebo-controlled study evaluated gastric-retentive gabapentin in 158 individuals who had chronic pain from post-herpetic neuralgia for at least 3 months. Patients were given 1,800 mg gabapentin ER once daily in the afternoon or 600 mg in the morning with 1,200 mg in the afternoon (twice-daily dosing) or placebo. Efficacy outcomes included changes from baseline on the pain intensity numeric rating scale (average daily pain) and average daily sleep interference score. The authors found statistically significant reductions in pain scores at all time points and as early as week 1 post-treatment in the gabapentin ER twice-daily group compared with the placebo group. But there was no significant reduction in pain scores in the once-daily gabapentin ER group compared with the placebo control, although a trend was noted. It was concluded that although ideal, once-daily gabapentin ER dosing may result in plasma levels that fall below the therapeutic range before the end of the 24-hour dosing period. Overall, the proportion of responders with at least a 50% reduction in pain score in the gabapentin ER twice-daily group (28.8%) was comparable with that reported in the immediate-release gabapentin studies (32.2%)[156] and in the pregabalin studies (150 mg/day, three times a day [26%], or 300 mg/day three times a day [28%]).[172] The incidence of adverse events was not statistically different between the placebo group and either of the gabapentin ER groups (once- or twice-daily), and it did not appear to be dose-dependent.[173]

XP13512: Gabapentin enacarbil

A novel pro-drug of gabapentin, XP13512/GSK 1838262 ((±)-1-([(α-isobutanoyloxyethoxy)carbonyl]-aminomethyl)-1-cyclohexane acetic acid) was recently developed. This drug has enhanced absorption in the large intestine, allowing an extended-release formulation.[174] Four clinical studies (two immediate-release [IR] formulation studies and two extended-release [XR] formulation studies) have evaluated the bioavailability of the drug. In the first IR study, XP13512 was administered to healthy adults. Five groups of 10 subjects were randomized to receive the pro-drug or placebo in a double-blind fashion with five ascending pro-drug/placebo doses (200, 400, 800, 1,200, and 1,400 mg). Maximum blood gabapentin concentrations were noted at 2.5 h postadministration. Bioavailability was consistently high (>67%) across all doses. In the second IR study, twice daily dosing (350 mg–2,100 mg) was given. Steady state concentrations of XP13512 were found proportional to the oral dose range. In addition, the bioavailability of gabapentin from XP13512 was consistently high (>72%) across the dose range. Blood concentrations of the intact pro-drug after oral dosing were low. In the first XR study, plasma exposure to gabapentin was higher post-XR treatment than after an equimolar dose of oral gabapentin. The time to maximum concentration (T-max) of gabapentin was substantially greater in the subjects given XP13512 than in subjects given oral gabapentin. In another XR study, plasma gabapentin was proportional to the XP13512 dose over the range studied (300 mg–1200 mg); bioavailability was increased in the presence of food. Sustained delivery was noted at all dose levels. Overall, both IR and XR formulations of XP13512 were well tolerated without serious adverse events. Minor adverse events reported included dizziness, headache, and sedation. Minor event reporting was similar for oral gabapentin, except for increased dizziness in the IR formulation of XP13512, perhaps due to rapid absorption. The XR formulation, although with higher peak gabapentin concentrations than oral gabapentin, actually had similar adverse events compared with oral gabapentin.[174]

Given its increased absorption and more predictable gabapentin exposure, its reduced inter-patient variability, and its reduced-dosing frequency, XP13512 may become an important option in our toolbox of upcoming neuro-

pathic agents. This novel extended-release pro-drug would be ideal for patients requiring prolonged clinical exposure, such as patients with restless leg syndrome, using a single daily dose. Use of the XR formulation may dramatically improve treatment compliance.

GlaxoSmithKline announced results from a phase II clinical trial of XP13512 for painful diabetic neuropathy in adults in April 2009 (Phase II Results for GSK1838262 [XP13512] Reported for Neuropathic Pain Associated with Diabetic Peripheral Neuropathy; *Medical News Today*; article date, 4/29/2009; http://www.medicalnewstoday.com/articles/148026.php). There were 421 patients who were enrolled in a 14-week, double-blind, placebo-controlled study and were randomized to receive either 1,200 mg/day, 2,400 mg/day, or 3,600 mg/day of XP13512 in divided doses twice-daily; 300 mg/day pregabalin as an active control in divided doses three times daily, or a placebo. The primary endpoint was a change from baseline on the Pain Intensity-Numerical Rating Scale (PI-NRS). Both the pregabalin active control and XP13512 failed to show a statistically significant benefit when compared with a placebo. These results may be due to an unusually high placebo response. Therefore, efficacy conclusions are difficult to draw. XP13512, at all doses, was well tolerated in the study. Dizziness and somnolence were the most common reported adverse events.

The efficacy of XP13512 was also recently tested in a randomized, double-blind, placebo-controlled study in a population of patients with moderate-to-severe primary restless leg syndrome.[175] There were 222 patients who were randomized to 1,200 mg/day of XP13512 once-daily or a placebo, and 192 patients completed the study. At week 12, there was a greater improvement in international restless leg syndrome scores. Significant treatment effects were noted as early as 1 week, the earliest time point measured, in the treatment group. More patients treated with XP13512 (76%) were responders compared with placebo (39%) ($p < 0.0001$). The medication was generally well tolerated; mild-to-moderate side effects, including somnolence and dizziness were reported.[175]

Pregabalin

Pregabalin, S-enantiomer of racemic 3-isobutyl GABA, is a second-generation anticonvulsant and structurally similar to gabapentin. The binding affinity of pregabalin for the $Ca_v\alpha_2\delta_1$ subunit, however, is 6 times greater than that of gabapentin, which makes pregabalin more clinically effective at lower doses.[176] Pregabalin is approved in the United States and Europe for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, and epilepsy as an add-on agent[177–180] (Table 1). In addition, pregabalin was approved by the FDA in 2007 as the first drug for the treatment of fibromyalgia[181] (Table 1).

Pregabalin is well tolerated, has predictable absorption across the gastrointestinal tract, and has minimal drug-drug interactions.[182] Clinical trials have been conducted to examine the efficacy of pregabalin in other chronic pain conditions (Table 2). At least seven published prospective, randomized clinical trials have documented its efficacy in postherpetic neuralgia and painful diabetic peripheral neuropathy with improvements in pain intensity scores, decreased sleep interference, and secondary outcome improvements.[182] The effects of pregabalin on patients with fibromyalgia are a current focus. These were first published in 2005[183] in an 8-week multicenter efficacy and safety clinical trial. Pain intensity, sleep, fatigue, and quality of life were measured outcomes. Pregabalin (at 450 mg/day) significantly reduced pain intensity on a 0 to 10 point scale as compared with a placebo ($p \leq 0.001$). Pregabalin (at doses of 300 mg/day and 450 mg/day) was reported to statistically improve sleep, fatigue, and global measures of change. At 450 mg/day, pregabalin also improved other secondary outcomes associated with health-related quality of life as measured in the Short Form-36 (SF-36) Health Survey. Adverse events were mostly mild, and the most frequently reported adverse events were dizziness and somnolence, although weight gain and peripheral edema were also reported.[183]

Pregabalin was also studied in combination therapy for pain management. It was used in a combinational treatment of fibromyalgia[184] in an open-label, 12-week study in 19 female patients already receiving therapy with quetiapine (76 mg/day). At the dose range from 75 mg/day to 300 mg/day, depending on the patient's tolerability, pregabalin was found to statistically improve the physical component of the SF-12 Health Survey, as well as the pain and tiredness in the awakening subscales of the fibromyalgia impact questionnaire. Six of 19 patients withdrew from the study, including 3 of them due to side effects.[184]

A multicenter study involving more than 700 patients evaluated the efficacy and safety of pregabalin in patients with fibromyalgia.[185] Patients were given 300, 450, or 600 mg/day in twice-daily dosing schedules for 13 weeks. All patients treated with pregabalin had statistically improved pain scores and patient global impression of change scores as compared with placebo treatments. Statistically significant improvements in secondary outcomes measuring sleep were also reported. Side effects were mild to moderate and the most frequently reported side effects were dizziness, somnolence, headache, infection, and weight gain. This efficacy and safety was similarly documented in another recently published trial.[186] A recent long-term multicenter double-blind, placebo-controlled randomized discontinuation trial (FREEDOM) in the fibro-

myalgia population demonstrated the durability (maintenance of response with pregabalin treatment relative to placebo) of pregabalin for this indication.[187] In this trial, individually-determined optimal pregabalin doses were determined with the hypothesis that the therapeutic response would persist longer. The trial included a 6-week, open-label pregabalin-treatment phase followed by a 26-week, double-blinded treatment with pregabalin or a placebo. Patients treated with pregabalin had significantly delayed time to loss of therapeutic response, defined as <30% reduction in pain from open-label baseline, versus patients receiving a placebo ($p < 0.0001$). Half of the placebo group had loss of therapeutic response by day 19, but half of the pregabalin group retained therapeutic effect and had not lost response by the end of the trial. At the end of the 26-week, double-blind treatment phase, 61% of the placebo patients met loss of therapeutic response criteria versus 32% of pregabalin-treated patients. One contemporary commentary proposes a fibromyalgia treatment strategy combining pregabalin with memantine in the clinical trial.[188] The latter is proposed as an agent that may slow down the loss of cephalic gray matter commonly observed as a comorbidity in chronic pain states.[189–194]

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