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Membrane Stabilizer Medications in the Treatment of Chronic Neuropathic Pain: a Comprehensive Review

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Abstract

Purpose of Review Neuropathic pain is often debilitating, severely limiting the daily lives of patients who are affected. Typically, neuropathic pain is difficult to manage and, as a result, leads to progression into a chronic condition that is, in many instances, refractory to medical management.

Recent Findings Gabapentinoids, belonging to the calcium channel blocking class of drugs, have shown good efficacy in the management of chronic pain and are thus commonly utilized as first-line therapy. Various sodium channel blocking drugs, belonging to the categories of anticonvulsants and local anesthetics, have demonstrated varying degrees of efficacy in the in the treatment of neurogenic pain.

Summary Though there is limited medical literature as to efficacy of any one drug, individualized multimodal therapy can provide significant analgesia to patients with chronic neuropathic pain.

Keywords Neuropathic pain · Chronic pain · Ion Channel blockers · Anticonvulsants · Membrane stabilizers

Introduction

Neuropathic pain, which is a result of nervous system injury or dysfunction, is often debilitating, severely limiting the daily lives of patients who are affected. Frequently, it is difficult to manage and as a result leads to the progression of a chronic condition that is, in many instances, refractory to medical management. Common causes of neuropathic pain include lumbar radiculopathy, diabetic peripheral neuropathy, and postherpetic neuralgia. While antidepressants and several anticonvulsant medications are widely instituted as first-line therapy, there is a lack of consensus regarding next-line therapy in patients who continue to experience pain. In this review, an overview of membrane stabilizing medications is presented. These medications have been shown to be effective in the management of chronic neuropathic pain.

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Sodium Channel Blocking Anticonvulsants

The sodium channel blocking class of drugs antiepileptic drugs has been proven useful in the treatment of neurogenic pain. Following insult to sensory neurons, there is well-documented aberrant expression of sodium channels on peripheral nerves. It is possible that the antinociceptive properties of these agents arise from countering this aberrancy [1]. Aside from sodium channels, each of the following agents has

unique ranges of activity. Some block calcium channels while others significantly modulate neurotransmitter levels. These additional, unique profiles may lend insight into best practice use and limitations of each individual agent in the management of neuropathic pain [2].

Phenytoin

Phenytoin (PHT) is a compound derived from barbiturates. It differs molecularly from barbiturates at the C5 position of the hydantoin molecule, at which PHT contains two phenyl rings rather than alkyl groups [3]. The mechanism of action has been historically understood as a sodium channel modulator, as it blocks virtually all subtypes of voltage-gated sodium channels (Na_V). Recently, PHT has also been shown to antagonize voltage-dependent L-type calcium channels and GABA-A receptors, thus suggesting a more complex mechanism of reducing neuroexcitability and conductance [4].

Phenytoin was the first non-sedative compound used to manage epilepsy. Its minimal hypnotic activity is thought to be attributed to the previously mentioned chemical modification. Many patients treated with PHT develop gingival hyperplasia, and this finding sparked research that illustrated wound-healing properties and examined its efficacy in treating diabetic foot ulcers [5]. Other adverse effects include dizziness, nystagmus, ataxia, gingival hyperplasia, folate deficiency, and polyneuropathy. As with many antiepileptic compounds, drug-induced osteopathy is a potential adverse effect, which is thought to be caused by the induction of cytochrome metabolism of vitamin D [6].

The efficacy of intravenous PHT in treating neuropathic pain was established in a double-blind randomized control trial, showing significant pain relief at a dosage of 15 mg/kg over a 2-h period. This pain relief significantly outlasted the infusion period and plasma half-life of PHT, supporting future studies to examine the efficacy of topical creams. A series of case reports by Kopsky et al. showed that 10% topical PHT cream was an effective treatment in reducing neuropathic pain in patients with chronic idiopathic axonal polyneuropathy (CIAP) and painful diabetic neuropathy (PDN) [7]. In a single-blind response study, Kopsky et al. established that 10% PHT cream, when compared to a placebo, provided statistically significant relief in a cohort of 70 patients with neuropathic pain. The mean daily application in this group was 2.3 g, and no PHT plasma levels were detected in any patient. Over 65% of patients achieved a pain reduction of at least 50%, with an average duration of action around 8 h. The mean onset of action was around 15 min, which is significantly shorter than the days to weeks seen in other oral treatments [8••]. These findings of significant pain reduction, long duration of relief, and short onset of action all support the use of topical PHT as an effective treatment for neuropathic pain.

Carbamazepine

Carbamazepine (CBZ) is another antiepileptic compound with a wide range of molecular targets. The primary mechanism of analgesia is thought to be elicited through blockade of specific sodium channels found on peripheral neurons, restricting neuronal firing rates. It also inhibits calcium channels and NMDA/AMPA receptors, although only at concentrations significantly higher than the therapeutic range [9]. CBZ has also been shown to potentiate the analgesic effects of morphine, which is an effect consistent with many NMDA antagonizing agents [10].

The primary use of CBZ is in the treatment of idiopathic trigeminal neuralgia (ITN), for which it is the first line of treatment. The optimal starting dose is 100 mg PO bid, which should be increased 100–200 every week to reach a target dosing of 200–400 mg tid [11]. The maximum dose is 1200–1800 mg/day, although adverse cognitive effects are observed at doses as low as 800 mg and 1200 mg in females and males, respectively [12, 13]. HLA genotyping must also be taken into consideration when dosing CBZ. Certain genotypes, such as the *HLA-B*15:02* allele, which is common in individuals of Southeastern Asian descent, are highly associated with life-threatening dermatologic complications including Stevens–Johnson syndrome and toxic epidermal necrolysis [14]. Other adverse effects of CBZ include ataxia, fatigue, drowsiness, memory problems, and impaired sleep, among others. Agranulocytosis is seen in some patients with chronic administration and is thought to be related to suppression of colony-stimulating factor and impaired neurogenic inflammation [15, 16].

Although there are numerous adverse effects, CBZ appears to have a role in the management of neuropathic pain associated with various conditions. Wiffen et al. established a slight efficacy of carbamazepine in treating PDN. Patients treated with 600–3600 mg/day CBZ reported higher percentages of pain benefit when compared to the control group. While this finding was statistically significant, it was regarded as third tier due to small study sizes and a wide range of doses [17]. A meta-analysis by Liu et al. compared interventions for the treatment of neuropathic pain in Guillain-Barre syndrome, which included CBZ. A statistically significant reduction in pain scoring and need for rescue analgesics was found by the third day of treatment when compared with the placebo, although a separate randomized control trial showed better outcomes associated with gabapentin treatment over CBZ [18]. While it is a mainstay in the treatment of ITN, further research is needed to evaluate the use of CBZ in treating other causes of neuropathic pain.

Oxcarbazepine

Like CBZ, oxcarbazepine (OXC) is thought to exert its effect through blockade of voltage gated sodium channels. Patel et al. showed that OXC reduces spontaneous activity in the ventral posterolateral thalamus in rats with spinal nerve

ligations. This is thought to be achieved though peripheral suppression of sodium channels found on hyperactive primary afferent nerves [19]. Recent studies suggest additional activity against various calcium channels as well [20].

Unlike CBZ, OXC has a low propensity for cytochrome induction and is metabolized renally, making it a useful alternate agent to treat ITN. Both OXC and its metabolite 10-hydroxycarbazepine are shown to be active, but the later accumulates to higher amounts throughout chronic therapy, so OXC is regarded as a pro-drug. In treating neuropathic pain the starting dose of OXC is 300 mg PO bid, which can be increased in small increments as tolerated to a maximum daily dose of 1200–1800 mg/day [12, 21]. Similar to CBZ, dosage and gender appear to be predictive of toxicity. Besi et al. established that females were 50% likely to experience a toxic dose at 1200 mg, where males where only 20% likely at a higher dose of 1600 mg. Therefore, renal function and gender should be taken into consideration when dosing [13].

OXC and CBZ have a similar adverse effect profile, including drowsiness, ataxia, fatigue, and other cognitive effects. In addition, both drugs are associated with drug-induced SIADH [22]. However, OXC is significantly less likely to cause the serious dermatologic complications and agranulocytosis associated with CBZ use, making it an attractive alternative for the management of ITN. The majority of literature shows no difference in the efficacy of these two drugs, and OXC is used in Scandinavian countries as the first line of treatment [13]. While useful in ITN, OXC is relatively ineffective in treating other causes of neurogenic pain. Various studies have shown OXC to be ineffective in treating PDN when compared to a placebo, one of which showing a higher rate of adverse effects compared to other treatments [1, 17]. In patients with fibromyalgia OXC has little to no effect on pain reduction [23].

Valproic Acid

Of the sodium channel blocking drugs, valproic acid (VPA) perhaps has the widest range of activity. In addition to functioning as a membrane-stabilizing agent through the blockage of voltage gated sodium channels and T-type calcium channels, it also affects neurotransmitter levels, acting as a GABA-agonist. This is propagated through inhibition of GABA transaminase and increasing the activity of glutamic acid decarboxylase [24]. VPA also has unique antiinflammatory properties. Recent research regarding VPA's role in migraine prophylaxis confirmed that it significantly reduces inflammation through modulating transcription of NF-κB gene products, functioning as a histone–deacetylase inhibitor [25]. It also has proven efficacy in aborting medication–overuse headaches and migraines, which is thought to be related to its antiinflammatory properties [26, 27].

VPA has been shown effective in treating post-herpetic neuralgia (PHN) and PDN. The adult dosage is 500 mg PO bid for treating both conditions, but it should be started at 500 mg PO QD in the first week for PHN and subsequently increased to full dosage [28, 29]. Although some studies have shown VPA to have questionable efficacy in treating other causes of neuropathy, a case series by Pirapakaren et al. showed significant pain relief in patients with ITN, post-surgical neuropathy, and lumbar radiculopathy. The authors have suggested that 400 mg PO bid VPA can be used as a second-line therapy in the event that first-line therapy for neuropathic pain is not tolerated or ineffective [2]. Interestingly, Hamada et al. showed that co-administration of calcitonin with VPA elicited significant increases in pain threshold than VPA alone in mouse models, suggesting that calcitonin somehow synergistically increases VPA's antinociceptive properties [30].

The adverse effects of VPA include gastrointestinal disturbance, weight gain, tremor, teratogenicity, and hepatotoxicity. Valproate-induced hyperammonemic encephalopathy (VHE) is a rare but serious complication associated with chronic use in select patients. It presents variably, with potential behavioral changes, lethargy, ataxia, sudden neurologic deficits, and seizures [31]. Risk factors for developing VHE include polypharmacy with multiple antiepileptic devices and poor nutrition [32]. Neither dosage or plasma level of VPA was found to be predictive of VHE events, but diffuse slowing and epileptiform discharges are associated findings on EEG [33]. It can be treated with L-carnitine 50–100 mg/kg/day PO or IV. VPA is also associated with drug-induced pancreatitis, which is exceedingly rare but carries a high mortality rate [34].

Sodium Channel Blockers: Local Anesthetics

The activity of sodium channels is the central component of electrical signal propagation along neuronal axons. As such, their activity is key in understanding neurogenic pain. The mechanism, efficacy, and safety of sodium channel blocking local anesthetics have thus been heavily investigated as a therapeutic modality for the management of chronic neuropathic pain.

Lidocaine

Lidocaine alters the propagation of nerve signals by blockage of fast voltage-gated sodium channels along the axon. Blockade of these ion channels raises the depolarization threshold, decreasing the likelihood of a signal propagation, though the exact mechanism for its analgesic properties when given intravenously is still somewhat unknown [35]. The dosing of lidocaine depends on the route of administration. Many studies have examined the effects of systemic lidocaine for treatment of neuropathic pain. In a study conducted by Ferrante et al., 500 mg of lidocaine intravenously infused at a rate of 8.35 mg/min over 60 min, while Prezeklasa-Muszynkska et al. dosed the infusion of lidocaine to be 5 mg/kg of body weight over 30 min, though other studies

used doses as small as 1.5 mg/kg of body weight over an hour [35–37]. When investigated in its topical form, Meier et al. chose to administer lidocaine patch 5% [38]. At therapeutic doses, lidocaine poses very little risk for adverse effects, though due to lidocaine's various routes of administration, it is important for health care providers to monitor total lidocaine administration to avoid toxic levels in the blood, which is usually 4.5 mg/kg [39–41]. Adverse effects that have been associated with lidocaine use include arrhythmias, other heart rate disorders, and nerve toxicity [39, 42]. Overall, the risk of adverse effects is low with lidocaine use, and the adverse effects that occur are overwhelmingly non-serious and mild to moderate in severity [43••, 44].

Lidocaine's multiple administration modalities (patch, cream, injection, etc.) make it a convenient agent for neuropathic pain management. Lidocaine has been shown useful in the treatment of neuropathic pain and other disorders. For instance, in a study review conducted by Challapalli et al., 32 controlled clinical trials were selected and found that lidocaine and oral analogs were superior in pain relief to placebo and showed similar efficacy without some of the adverse effects as compared to other drugs traditionally used for neuropathic pain (carbamazepine, amantadine, gabapentin, etc.) [45]. Lidocaine's use has also been implicated in other pain disorders, such as trigeminal neuralgias and various headache subtypes. In a study by Marmura et al., lidocaine's use in chronic daily headaches and chronic cluster headache showed a decrease of 4 points on a pain scale post IV lidocaine therapy, with low incidence of adverse events (pretreatment score avg. 7.9, posttest treatment score avg. 3.9) [44].

The combination of lidocaine's wide range of administration modalities, favorable side effect profile, and the increasing amount of research that supports its efficacy, has exhibited lidocaine's effective use in the treatment of neuropathic pain.

Mexiletine

Mexiletine, an analog of lidocaine, is classified as a class IB drug in the Vaughan-Williams classification of antiarrhythmic drugs, exerts actions as an antagonist at sodium channels [46]. Mexiletine, and other Class IB drugs, show a heightened specificity for sodium channels in the depolarized state, which as a result confers a unique quality of having modest effects on cardiac action potential as compared to agents in other antiarrhythmic classes. Mexiletine's action at peripheral nerves are predominantly exerted through blockade of sodium channels, subsequently altering resting membrane potential and inhibiting propagation of signal impulses [46]. Some adverse effects that have been associated with mexiletine include nausea, dizziness, and tremors [47–49].

Mexiletine's use for specific disorders has been shown to improve symptoms and to decrease pain. Statland et al. studied mexiletine's use in non-dystrophic myotonia, a group of diseases marked by delayed muscle relaxation, joint stiffness and pain, and reported a drastic decrease in muscle stiffness [50]. Mexiletine's usefulness in the treatment of non-dystrophic myotonia may be due to mexiletine's action decreasing fiber excitability found in common mutations associated with non-dystrophic myotonias [46]. Additionally, in a study conducted by Cregg et al., mexiletine was found to shift pathologically-hyperpolarized voltage-dependence of steady state activation towards more normal values, in certain gain of function sodium channel mutations associated with the condition erythromelalgia, a condition marked by severe pain and redness of the feet and hands [51].

Mexiletine's efficacy in neuropathic pain is somewhat limited. It is often considered a third-line drug in the line of neuropathic pain treatment [52]. Its use in conditions such as central pain, post-herpetic neuralgia, and diabetic neuropathy has shown it to be inefficacious or shown to have discrepant results [53]. But mexiletine use in more specific conditions such as non-dystrophic myotonias and erythromelalgia has shown more promising results, though more research will be needed to validate these preliminary findings and elucidate other conditions for its potential use.

Lamotrigine

Lamotrigine, a triazine derivative, belongs to a class of drugs which blocks voltage-sensitive sodium channels. Blockade of these channels subsequently leads to stabilization of the neuronal membranes, preventing the release of neuroexcitatory substances glutamate and aspartate. Lamotrigine has also been noted to have antagonistic actions at calcium channels, which also aid in stabilizing the neuronal membranes. And while lamotrigine main therapeutic use in treatment of epilepsy, it has been implicated in the use of bipolar disorder, neuropathic pain, trigeminal neuralgia, and various headache subtypes [54–56]. Most studies investigating the use of lamotrigine for the use of neuropathic pain started with initial doses ranging from 125 to 200 mg but were titrated up to a maximum dose of 400 mg per day [54, 57]. Lamotrigine has been associated with various skin conditions, including rash, Steven–Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome but has also been associated with side effects such as vision disturbances, insomnia nausea, dry mouth, dry mouth, and nightmares [58–62].

While established as an efficacious and reasonable option for epilepsy, lamotrigine has not shown to be an efficacious pain modulator [54, 63]. A recent review by Wiffen et al. evaluated 12 studies with over 1500 participants, between three tiers of evidence, examined a potential role for lamotrigine in treating neuropathic pain and found there was no conclusive evidence to suggest lamotrigine was efficacious in treating neuropathic pain [54]. Though studies by Agrawal and Joshi seemed to indicate a role for lamotrigine for neuropathic pain in spinal cord injuries, the clinical importance of

these findings has been scrutinized [64, 65]. Despite this, the use of lamotrigine in other conditions has shown more promising results, such as a potential role for lamotrigine in treatment of trigeminal neuralgia. One such study conducted by Shaikh et al. found lamotrigine to be an effective treatment option for trigeminal neuralgia, with over 67% percent of their study sample responding positively to treatment [66]. Findings supporting the use of lamotrigine for trigeminal neuralgia and neuralgia form headaches have been reported in studies conducted by authors D'Andrea et al., Costa et al., Solaro et al. and Garcia, with a side effect profile that is more favorable when compared to carbamazepine the standard of treatment for trigeminal neuralgia [57, 67–69].

Calcium Channel Blockers

Gabapentin

Gabapentin is a gamma-aminobutyric acid (GABA) analog. It structurally similar to GABA and features an additional cyclohexyl group. The mechanism of action is incompletely understood as gabapentin does not alter GABA binding, uptake, or metabolism. Gabapentin is thought to inhibit voltage-gated calcium channels containing α2δ subunits and may act as a potent activator of KCNQ3 and KCNQ5 potassium channels [70]. Standard adult dosing for the management of neuropathic pain ranges from 300 to 600 mg PO three times daily with a maximum daily dose of 1800 mg/day. Gabapentin is also used in the management of partial seizures, post-herpetic neuralgia, alcohol dependence, fibromyalgia, as well as additional off-label treatments with alternative dosing for these uses. Adverse effects include somnolence, fatigue, ataxia, diplopia, nystagmus, constipation, and dry mouth among others. Additionally, in a 2018 survey, approximately 41% of sampled patients reported sexual dysfunction including erectile dysfunction, anorgasmia, and loss of libido following gabapentin treatment [71]. According to this study, these effects occurred independently of dosage and resolved fully within weeks of discontinuing gabapentin.

Optimal use of gabapentin remains the subject of ongoing research. A recent meta-analysis by Enke et al. evaluated nine trials comprised of 859 unique patients and found that gabapentin, pregabalin, and topiramate were no more effective than placebo in the short-term management of chronic low back pain or lumbar radiculopathy but were associated with an increased risk for adverse effects [72]. Despite these findings, Shamagel et al. report that, of over 5000 surveyed adults with chronic low back pain, approximately 7% consumed gabapentin or pregabalin within 30 days of the time of survey [73]. This may have significant ramifications because gabapentin use has been linked to increased perioperative naloxone requirement for excessive sedation and respiratory depression when co-administered with narcotics [74]. Use is also independently associated with daytime sedation, impaired driving, and impaired cognition, though these effects are reduced with gastroretentive formulations such as Gralise [75].

Pregabalin

Like gabapentin, pregabalin is a GABA analog that affects voltage gated calcium channels within the central nervous system. The exact mechanism of action is unknown. However, recent inflammatory pain models suggest that pregabalin and gabapentinoids utilize $\alpha_2\delta$-dependent voltage-gated calcium channels to suppress the release of central nervous system neurotransmitters within the dorsal horn [76]. Presently, researchers are unaware of any interactions between pregabalin and opiate receptors, cyclo-oxygenase enzymes, or central nervous system sodium channels [76].

Pregabalin has > 90% bioavailability, making oral preparations highly effective. Current dosing formulations range from 25 to 300 mg and include extended release options [77]. Adult dosing for diabetic neuropathy is 50–100 mg PO bid, dosing for neuropathy secondary to spinal cord injury is 75–300 mg PO bid, and dosing for post-herpetic neuralgia is 150–300 mg PO bid/tid. Pregabalin may also be used in the treatment of fibromyalgia and partial seizures. Pregabalin exhibits minimal protein binding and is renally excreted in its unmetabolized form. Renal dosing modifications are necessary according to patient creatinine clearance. Well-known adverse effects include constipation, dry mouth, drowsiness, difficulty concentrating, and dizziness. Additionally, in a recent population-based cohort study, Ortiz de Landaluce et al. found an association between treatment with pregabalin or gabapentin and new diagnosis and treatment of atrial fibrillation among elderly patients who were previously without diagnosed cardiovascular disease [78]. The strength of this association was found to increase with increasing dose [78].

Despite these adverse effects, pregabalin may still benefit patients with perioperative and chronic pain. In a 2018 phase 1, randomized, double-blind, controlled trial evaluating 24 healthy male subjects without chronic pain, pregabalin lowered visual analog scale (VAS) evoked pain scoring and laser evoked potential "peak-to-peak" amplitudes when compared to a placebo [79]. In a second randomized, double-blind study, Ibrahim et al. report that the use of pregabalin to augment dexmedetomidine during conscious sedation for bronchoscopy was associated with significantly higher scores in patient sedation, improved heart rate and mean arterial pressure, and improved pulmonologist and patient satisfaction. Augmentation with pregabalin was also associated with shorter PACU stays and reduced analgesic requirements [80].

Zonisamide

Zonisamide is a sulfonamide used in the treatment of epilepsy and Parkinson's disease. It also has off-label applications as a weight-loss medication and in the treatment of chronic migraines. Medication is available in 25 mg, 50 mg, and 100 mg capsules. In the context of renal impairment, conservative dosing is recommended.

Several recent publications examine the mode of action and utility of zonisamide. Unlike gabapentin and pregabalin, zonisamide is a monoamine oxidase B (MAO-B) inhibitor. Zonisamide targets voltage-gated sodium channels in the central nervous system and may reduce the release of inflammatory cytokines in the microglia and striatum. Through this mechanism, it contributes to decreased neuroinflammation within the central nervous system [81].

Zonisamide has a developing role in the management of neuropathic and migraine-related pain. In a randomized, controlled trial comparing zonisamide and sodium valproate, Assarzadegan et al. report that there was no statistically significant difference in migraine frequency between the two treatment branches. However, zonisamide was associated with increased incidence of fatigue and weight loss while sodium valproate was associated with dizziness and weight gain [82]. These differing side effect profiles may be selectively targeted according to the needs of carefully selected migraine patients. Historically, Atli et al. suggested a role for zonisamide in the management of neuropathic pain [83]. However, a Cochrane review of zonisamide-related clinical trials found that the study was limited by small sample size and early withdrawal of participants, which expose the study results to potential inherent bias [84]. This Cochrane review found that there was an overall lack of first or second tier evidence among existing clinical trials that zonisamide may benefit patients with painful neuropathy. The review concluded that medication with stronger supporting evidence is available to patients and prescribers.

Ziconitide

Ziconitide is a synthetic conotoxin, which is modeled after a toxin originally isolated from *Conus magnus.* Presently, it is the only FDA-approved non-narcotic pain medication approved for intrathecal injection [85]. Ziconitide is a strong, selective inhibitor of N-type voltage-gated calcium channels including N-type calcium channels within the cerebral cortex and neurohypophysis. It benefits patients experiencing chronic, non-cancer-related pain by blocking the release of CNS neurotransmitters, particularly norepinephrine. Clinical use is also associated with decreased oral and cumulative opioid consumption [86].

Ziconitide has minimal inherent ability to cross the blood–brain barrier and therefore must be administered intrathecally to affect the central nervous system. It does not contain preservatives and is typically used as an intrathecal monotherapy [87]. Low blood–brain barrier permeability also confers the benefit of better analgesia with fewer systemic adverse effects. Dosing starts at a rate of 0.1 μg/h as a continuous infusion. This correlated with an initial dosing of 2.4 μg/day, and intrathecal delivery rate is then carefully monitored and titrated according to patient analgesic needs and side effects. The recommended maximum daily dose is 19.2 μg/day or a rate of 0.8 μg/h.

The metabolism of ziconitide involves cleavage of peptide bonds by endopeptidase and exopeptidase after crossing the blood brain barrier into systemic circulation [88]. There is minimal degradation within the cerebral spinal fluid. Present use is somewhat limited by patient inconvenience due to the need for a carefully titrated infusion pump as well as from adverse effects including hallucinations, memory loss, confusion, gait disturbance, depression, and syncopal or pre-syncopal events [89]. Many patients treated with ziconitide discontinue ongoing treatment. For this reason, ziconitide is primarily used in the treatment of chronic pain that is refractory to more traditional approaches such as intrathecal morphine, systemic opioids, anticonvulsants, and antidepressants [87].

Magnesium

Magnesium is a physiological cation with normal plasma concentrations of 1.4–2.2 mEq/L [90]. Hypomagnesemia may occur in the perioperative period or periods of prolonged fasting and can result in tetany, paresthesia, and seizures. Hypermagnesemia is rare outside the context of impaired renal function or iatrogenic causes and may result in dizziness and loss of deep tendon reflexes at concentrations of 4–5 mmol/L or cardiovascular and pulmonary arrest in concentrations exceeding 8 mmol/L and 6 mmol/L respectively [90].

Magnesium sulfate has been used in the treatment of cardiac arrhythmias, preeclampsia, and seizure prophylaxis. However, its use as a muscle relaxant and adjunct to perioperative anesthesia and analgesia is gaining traction as an opioid-sparing pain management modality. Magnesium potentiates intraoperative and postoperative anesthesia and analgesia by contributing to NMDA receptor blockade in a voltage-dependent manner. Intraoperative dosing includes a loading dose of 30–50 mg/kg, which may be followed by an infusion dose of 6–20 mg/kg/h until completion of the surgery [90].

Several recent studies evaluate perioperative use of magnesium sulfate. Following a randomized, double-blind, clinical trial, Farzanegan et al. found that adding magnesium sulfate to epidural morphine and bupivacaine reduces opioid consumption during thoracotomy. In this study, 80 patients received bupivacaine 12.5 mg and morphine 2 mg before randomly receiving an additional dose of either magnesium sulfate 5 mg or an equivalent volume of normal saline. Patients receiving magnesium reported lower visual analog scale (VAS) scores at 0, 2, and 4 h postoperatively, initiated patient controlled analgesia later, and consumed less cumulative narcotics

[91]. Similarly, in a 2018 prospective, randomized clinical trial, Kizilcik et al. found that magnesium sulfate reduced cumulative opioid consumption and pain scores among obese patients undergoing sleeve gastrectomy when compared to controls not receiving magnesium [92]. Abdelaziz et al. also have reported that the addition of magnesium to bupivacaine for pectoral nerve blocks during breast surgery resulted in lower patient-reported pain scores postoperatively [93].

These analgesic effects allow care providers to reduce perioperative narcotic consumption and improve patient pain scores with less sedation. Magnesium sulfate is also cost effective and has a high therapeutic index [93]. Considering these findings, magnesium may have an expanding role in potentiating anesthetics and analgesics. Additional research is needed to evaluate the role of magnesium as a solitary modality.

Conclusion

The pharmacologic mechanism of neuropathic pain remains poorly understood and continues to be investigated. While gabapentinoids stand out as one of the best therapeutic options for patients with chronic neuropathic pain, their use as monotherapy is limited. Though there may be no perfect therapeutic option for all given patients, experience shows that good effect may be achieved from individualized strategies of multimodal therapy. As such, it is important for clinicians to be aware of the many available classes of membrane stabilizing drugs that may help to improve symptoms in patients with chronic neuropathic pain.

Compliance with Ethical Standards

Conflict of Interest Omar Viswanath, Ivan Urits, Mark R. Jones, Jacquelin M. Peck, Justin Kochanski, Morgan Hasegawa, and Best Anyama declare no conflict of interest. Dr. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc. and Merck. and declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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