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Focus Article

Old Friends With New Faces: Are Sodium Channel Blockers the Future of Adjunct Pain Medication Management?

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Abstract: **Providers are being asked to decrease the emphasis and overutilization of long-term opioid therapy, but many are left without proper guidance on appropriate utilization of nonopioid therapies. Furthermore, therapeutic options are quite limited and many providers lack confidence in distinguishing available alternatives. When first-line therapy has failed in a patient, there is an apparent lack of knowledge on how to proceed with choosing subsequent therapy. To choose among alternative agents, an understanding of pharmacology, pharmacokinetics, and efficacy in targeting various pain conditions is necessary. This article focuses on the use of the carboxamide class of sodium channel blockers (carbamazepine, oxcarbazepine, eslicarbazepine) for adjunct pain medication management including research updates in pharmacology, pharmacokinetics, and current evidence for pain along with promising areas of research. It is an evidence update for clinical use of sodium channel blockers, clarifies misconceptions regarding their use, and highlights emerging research for improved pain targets that justifies additional study. We performed a complete review of the literature using the search terms, "oxcarbazepine," "carbamazepine," and "eslicarbazepine" in conjunction with "pharmacokinetics," "adverse effects," "pharmacology," "voltage-gated sodium channel subtype," "neuropathic pain," "inflammatory pain," "metabolism," "epoxide metabolite formation," "drug interactions," "CYP450 interactions," "pain phenotype," and "chronic pain management." Databases searched included PubMed and Google Scholar. Package inserts were used for drug structure illustration, adverse reactions, and bioavailability. Pharmacology and pharmacokinetic data were taken from randomized controlled trials evaluating this area as well as in vitro published results. For validity, only peer-reviewed literature was included. Evidence for sodium channel blockers in chronic pain management was limited. This review focuses on highlighting the data available for the use of sodium channel blockers for certain pain syndromes as well as underutilized potential. Emerging literature on sodium channel subtypes and their connection to neuropathic, inflammatory, and mechanical pain transmission is elucidated. The authors also scrutinize literature surrounding the pharmacokinetics of oxcarbazepine and eslicarbazepine to provide clearer guidance to the significance of any drug interactions and refute assumptions made on the basis of structural similarity to carbamazepine and its known undesirable drug interactions. Side effect profiles are outlined and compared, emphasizing the differences between agents. Sodium channel blocker doses used in certain pain syndromes are outlined with a call for further research to better understand their place in chronic pain management. Identification of sodium channel subtypes with links to specific pain conditions and the ability to target them hints**

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at the potential for truly individualized therapy. Sodium channel inhibitors are underutilized on the basis of available evidence, and emerging research has identified this area as promising for additional clinical trials to better guide clinical practice.

Perspective: ***This article provides a review of the pharmacology, evidence for pain management, and pharmacokinetics of oxcarbazepine, carbamazepine, and eslicarbazepine. There is a disparity in evidence using sodium channel blockers for pain and this article highlights the potential that is currently underutilized. The authors believe this will catalyze interest for further studies.***

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Key words: *Oxcarbazepine, carbamazepine, eslicarbazepine, sodium channel blockers, adjunct therapy, chronic pain management.*

Chronic pain affects more than 100 million people in the United States every year, with 30 to 40 million reporting moderate to severe pain daily.[38] The lack of appropriate treatment and optimal care is multifactorial, however, poor understanding of appropriate therapies, namely nonopioid pain medications plays a significant role.[44] Providers are being asked to decrease the use of long-term opioid therapy, but many are left without proper guidance on appropriate utilization of nonopioid therapies.[61] Furthermore, therapeutic options are quite limited and many providers lack confidence in distinguishing available alternatives.[45] It is imperative that chronic pain be addressed and managed with therapy specific to the pain syndrome. Although opioids may be indicated for some patients, it is difficult to achieve pain control and decrease reliance on opioid therapy without a thorough understanding of how to choose nonopioid therapies. It is essential, therefore, to understand the benefits and risks of each therapeutic alternative and adjunct agent to combat the current opioid epidemic as well as sufficiently manage chronic pain.

Targeted approaches are being encouraged to treat pain syndromes on the basis of the etiology.[38] In addition to examining pain pathology, providers are being asked to characterize pain on the basis of nociceptive, neuropathic, inflammatory, somatic, or visceral symptomatology.[26] When distinguished, targeted medication management is key. Many are generally familiar with first-line therapies for inflammatory and neuropathic pain. However, when first-line therapy has failed in a patient, many providers have expressed that they lack the expertise to effectively differentiate or use subsequent therapeutic treatment options.

One class of medications that may currently be underutilized as an alternative for pain is voltage-gated sodium channel (Nav) blockers, specifically the carboxamide subclass, which includes carbamazepine (Tegretol; Novartis Pharmaceuticals Corp,

East Hanover, NJ), oxcarbazepine (Trileptal; Novartis Pharmaceuticals Corp), and recently eslicarbazepine (Aptiom; Sunovion Pharmaceuticals Inc, Marlborough, MA). This may be because of limited experience and data compared with first-line therapies. However, to appropriately manage pain, providers must become more familiar with second- and third-line medications and develop an understanding of where each class of medications fits into therapy. To choose among alternative agents, an understanding of pharmacology, pharmacokinetics, and efficacy in targeting various pain conditions is necessary. This article updates evidence for clinical use of sodium channel blockers, clarifies misconceptions regarding their use, and highlights emerging research for improved pain targets, which justify additional study.

Pharmacologic Targets

Sodium Channels

Voltage-gated sodium channels have been identified as contributing to pain syndromes through enhanced electrical currents and increased sodium channel density at sites of injury, both mechanisms leading to hyperexcitability and increased pain transmission.[16,34,35] There are 9 identified Nav subtypes (Nav 1.1–1.9) and multiple Navs have been linked to transmission of inflammatory, nociceptive, and neuropathic pain.[5,15,16,35,37,47,54,65,67] Furthermore, specific Navs have been identified recently with correlations to specific types of pain indicating that targeting overactive channels may be an oversimplification of the complex biological process involved in pain signaling.[37,65,67] Please see Fig 1 for Navs linked to pain and associated pain syndromes.

Nav 1.9 is found primarily distributed in the peripheral nervous system whereas Nav 1.8 is mostly distributed in the C-fibers of the dorsal root ganglia; however, there is evidence to support channel presence of Nav 1.7, Nav 1.8, and Nav 1.9 in dorsal root ganglia neurons with preferential small-diameter neurons, most of which are nociceptors,[15,18,54] thereby highlighting their involvement in pain transmission. Sodium channel subtypes are categorized as tetrodotoxin-resistant (TTX-R) or tetrodotoxin-sensitive. Nav 1.8 and Nav 1.9 are known to be TTX-R.[54] TTX-R currents have been shown to be largely involved in current transmission in nociceptive neurons, which is dynamically adjusted by response to injury.[54,65] Increased TTX-R channel activity was found in inflammation-linked dorsal root ganglia neurons.[54] Inflammatory mediators have also been shown to upregulate Nav 1.8 and Nav 1.7 and were linked to increased expression and enhanced current induction of Nav 1.9, suggesting involvement in the maintenance of inflammatory response.[5,54,65,67] Moreover, Nav 1.8 protein levels were shown to be elevated in dorsal root ganglia neurons surrounding inflamed limbs.[65] Studies allude to a link between Nav 1.7 in mechanical and inflammatory pain, Nav 1.8 to visceral pain, and Nav 1.9 to inflammatory pain transmission.[65,67] There have also been reports that suggest Nav 1.8 involvement in neuropathic pain.[52,65,67]

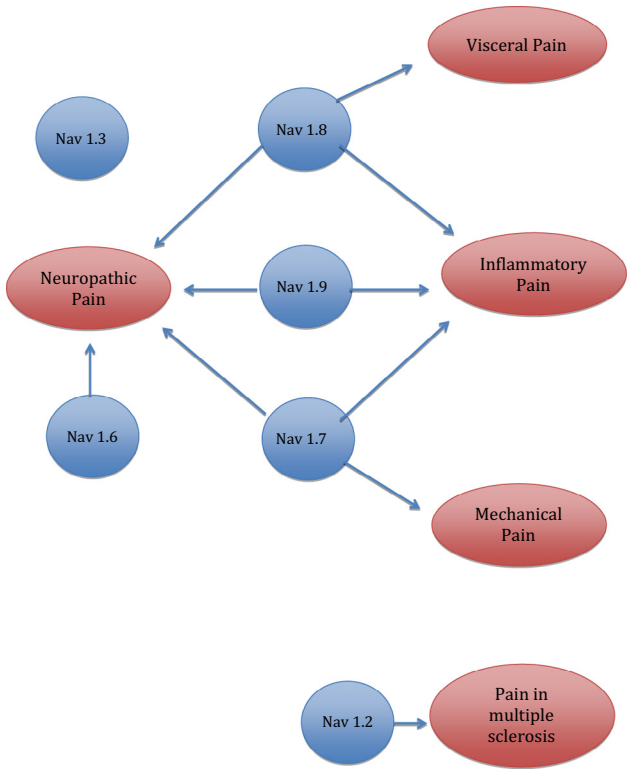


Figure 1. Sodium channel subtypes and associated pain syndromes.

Voltage-gated sodium channel alterations and expression in specific disease states and pain syndromes is also noteworthy. It is hypothesized that dysregulation of β_2-subunit of sodium channels is involved in the development of allodynia.[65] Nav 1.3 has been reported to be detectable only in injured nerves and found to be upregulated in dorsal root ganglia neurons by nerve injury.[16,65,67] Upregulation of Nav 1.3, Nav 1.6, Nav 1.7, and Nav 1.9 are observed in diabetic neuropathic pain.[65] Nav 1.3 has been shown to be upregulated at the site of peripheral nerve damage as well as upregulated in nociceptive dorsal horn neurons after experimental spinal cord injury[16]; it is believed that Nav 1.3 may be involved in neuropathic pain after nerve and spinal cord injury.[67] Nav 1.2 is mainly expressed on nonmyelinated axons and has been linked to multiple sclerosis (MS).[65]

Voltage-gated sodium channel mutations are also associated with multiple pain syndromes.[16,18,21,22] A well recognized mutation in Nav 1.7 is present in human erythromelalgia.[16,18] Mutations in Nav 1.7, Nav 1.8, and Nav 1.9 have been strongly linked specifically to neuropathic pain.[5,17,21,22,35,37,67] Nav 1.8 is expressed within Perkinje neurons in MS and deviations in sodium voltage-gated channel alpha subunit 10 (SCN10A) have been shown to predict the degree of cerebellar dysfunction in MS.[35] Last, there are data to support that in patients with paroxysmal extreme pain disorder, Nav 1.7, although activated by normal stimuli, does not deactivate appropriately, which leads to persistent sodium currents.[65,67]

Targeting of specific pain conditions through an associated sodium channel subtype is intriguing and has the potential to transform our current understanding and routine management of pain. Researchers are not entirely certain that pharmacologic agents can be successfully designed to selectively inhibit individual Navs. However, there is research in the pipeline for a drug that selectively targets Nav 1.7 as well as one that selectively targets Nav 1.8.[10,35,39] Recently, use of a drug designed to target Nav 1.7 (BIIB074) was evaluated in patients with trigeminal neuralgia in a withdrawal phase IIa trial.[70] The sample size was small and the results were not statistically significant, but nearly twice as many failures occurred in the placebo group compared with BIIB074. The results were promising and highlight the importance of further investigation.[70]

Additional research into which specific receptor subtypes are associated with each of the current pharmacologic agents is warranted and may guide focused research into specific pain types where data do not currently exist to guide therapy.

Pharmacology

Sodium channels undergo structural changes in response to depolarization; the channel phases through active (open), inactive, and resting or repriming states.[16] Agents must selectively inhibit Navs that are upregulated into an overactive state. Studies refer to overactive channels as the inactive state rather than the resting state of sodium channels.[62]

Current sodium channel blockers in the pharmacologic carboxamide subclass all bind to the α subunit of Navs. All 3 selectively inhibit sodium channels in the inactive state, carbamazepine and oxcarbazepine with an affinity >10 times that of the channel in resting formation, and eslicarbazepine with an affinity 3 times greater than that of carbamazepine.[1,2,11,51]

Carbamazepine, oxcarbazepine, and eslicarbazepine have similar chemical structures. Oxcarbazepine was designed to avoid the 10,11-epoxide metabolite of carbamazepine to which are attributed many of its serious side effects.[23,41] Eslicarbazepine is the (s)-isomer of the monohydroxy derivative (MHD), which is the active metabolite of oxcarbazepine most responsible for its activity.[32] Carbamazepine, oxcarbazepine, and eslicarbazepine have not shown specificity toward any particular Nav on the basis of current literature.

Pharmacokinetics

Carbamazepine and oxcarbazepine have nearly identical chemical structures, so it is understandable that many have assumed similar pharmacokinetic and adverse effect profiles. Understanding the differences, however, is crucial to appropriate use assessment. Oxcarbazepine differs from carbamazepine by one critical substitution to intentionally avoid the epoxide metabolite of carbamazepine and improve its overall tolerability. As a result, oxcarbazepine is metabolized very differently than carbamazepine. Carbamazepine uses the cytochrome p (CYP)450 enzyme system as a primary pathway of metabolism, leading to multiple drug interactions, including inducing its own

metabolism.[60] Because of their structural similarities, it was presumed that oxcarbazepine would display a similar pharmacokinetic profile. However, in contrast to carbamazepine, oxcarbazepine has only minor interaction with the CYP450 enzyme system.[23,28,58]

Oxcarbazepine has historically been considered a prominent CYP3A4 inducer, similar to carbamazepine. Pharmacokinetic studies have shown a lack of enzyme induction as well as autoinduction.[43,49] Additionally, pharmacodynamic studies specifically evaluating the effect of oxcarbazepine on 2 known CYP substrates, erythromycin and cimetidine, each showed no change in serum concentrations of erythromycin or cimetidine compared with monotherapy.[28] Conversely, other pharmacodynamics studies have raised questions about potential CYP3A4 induction properties. Oxcarbazepine was shown to reduce the area under the curve of felodipine by approximately 28% as well as enhance the metabolism of quinidine.[4,68] Many providers accepted the conclusion that oxcarbazepine was an inducer of CYP450 enzymes until one investigator proposed that induction properties may be dose dependent. The results of this evaluation validated that oxcarbazepine does not possess CYP3A4 induction properties until doses of ≥900 mg/d are used, and even at higher doses it is considered a weak inducer.[52] It is not entirely clear if the MHD metabolite is responsible for the induction properties; however, because oxcarbazepine is found almost entirely metabolized to MHD, it is most likely the true inducer. Eslicarbazepine reportedly showed no induction properties in vitro on human hepatocytes, but observed reduction in serum levels of simvastatin and birth control, lead to questions regarding the true pharmacodynamic profile.[8,24] Eslicarbazepine doses of ≥800 mg/d were used in each study evaluating the CYP3A4 induction properties potentially indicating a dose-dependent phenomenon similar to oxcarbazepine, but this has not yet been sufficiently confirmed in available studies.[8]

The MHD metabolite of oxcarbazepine was shown to inhibit CYP2C19 at normal concentrations and CYP2C9 at concentrations that exceed normal dosing of oxcarbazepine.[28] Similarly, eslicarbazepine has been shown to inhibit CYP2C19.[8] Few drugs use CYP2C19 for metabolism; therefore this inhibition has not translated to clinical significance. Eslicarbazepine, the s-isomer of MHD, predictably shows metabolism almost identical to oxcarbazepine.[69]

Pharmacodynamic studies evaluating the use of oxcarbazepine and eslicarbazepine in combination with warfarin have also been completed. Oxcarbazepine, even at doses of ≥900 mg/d, did not clinically affect international normalized ratio.[28,42] Eslicarbazepine at doses of 1,200 mg/d was shown to reach the level of statistical significance, but minimally affect serum levels of S-warfarin and there was no clinically significant effect on international normalized ratio.[8,64] Oxcarbazepine and eslicarbazepine have both been shown to decrease serum levels of birth control at higher doses.[4,8,24,51] This may be due to induction of CYP3A4, but it is also hypothesized that this interaction may stem from either inhibited absorption or potentially accelerated metabolic clearance.

Pharmacodynamic studies have clearly shown that oxcarbazepine does not share the risk of clinically significant drug interactions that are well characterized with carbamazepine. Any observed effects on drugs metabolized via CYP3A4 were minimally affected at doses of ≥900 mg/d. Refer to Table 1 for a summary.

Side Effects

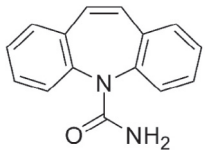
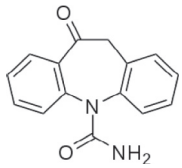
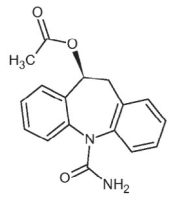
Cognitive impairment associated with carbamazepine has been directly linked to the concentration of the parent drug as well as the epoxide metabolite.[31] Because oxcarbazepine does not form an epoxide intermediate, it was expected that it would be better tolerated. Although the true population data are ambiguous, an analysis of head to head trials between patients treated with carbamazepine and oxcarbazepine highlighted oxcarbazepine as overall better tolerated.[12] Eslicarbazepine was expected to exhibit an even more tolerable profile by reducing the peak of MHD after administration; this has yet to be clinically validated.[50]

Carbamazepine has a warning for hematologic side effects, namely aplastic anemia or agranulocytosis.[11] It is not fully understood why oxcarbazepine and eslicarbazepine do not share this warning. This is often related to the lack of epoxide intermediate formation. However, a competing hypothesis attributes this to carbamazepine's binding and interaction with peripheral benzodiazepine receptors, which can be found on lymphocytes.[6] There is no definitive evidence to outline whether it is the parent drug or epoxide intermediate of carbamazepine that interacts with these receptors, but it is clear that oxcarbazepine and eslicarbazepine do not share this receptor activity. It is also believed that carbamazepine's activity at these peripheral benzodiazepine receptors helps mitigate its propensity to induce syndrome of inappropriate diuretic hormone.[48] Oxcarbazepine as well as carbamazepine carry a warning for drug-induced syndrome of inappropriate diuretic hormone and hyponatremia; however, this occurs significantly more often in patients treated with oxcarbazepine compared with carbamazepine, in a dose-dependent fashion.[3,32]

Another caution for use of these agents is dermatologic events. It is recommended that patients of Asian descent be tested for human leukocyte antigen-B*1502 and human leukocyte antigen-A*31:01 genes because this has been linked to a 10-fold increased risk of developing Stephens Johnson Syndrome.[11] Although there is a warning for potential dermatologic adverse events with oxcarbazepine and eslicarbazepine, it appears to be better tolerated. It was noted that 75% of patients who experienced serious dermatitis with carbamazepine tolerated oxcarbazepine.[32]

With each developmental improvement in these medications, there is a corresponding improvement in side effect profile. Previously, differing metabolic pathways were believed to be responsible for improved tolerability, but isolating the active moiety may be the key. As population data describing the tolerability of eslicarbazepine become available, it will add to the current

Table 1. Pharmacokinetic and Pharmacodynamic Comparison of Prescription Sodium Channel Blockers

	Carbamazepine[2,6,60] *(Tegretol)*	*Oxcarbazepine*[1,12,28,41,58,63] *(Trileptal)*	*Eslicarbazepine*[1,2,8] *(Aptiom)*
			
Receptor Activity	α Subunit of Navs; K_I resting: 984 μm; K_I inactivated: 47.8 μm	Site 2 of α subunit of Navs; K_I: higher affinity for inactive state	Site 2 of α subunit of Navs; K_I resting: 3,315 μm; K_I inactivated: 99.9 μm
Bioavailability	70% ↑ with food	No effect with/without food	No effect with/without food
Protein binding	70 to 80%	40%	30%
Metabolism	Hepatic: phase I CYP3A4 (major) CYP2C8 (minor)	Step 1: metabolism of oxcarbazepine by arylketone reductase to MHD Step 2: MHD metabolism: hepatic: phase I (CYP450-minor) approximately 4% to inactive metabolite Hepatic: phase II: glucuronidation	Hepatic: phase II Esterases, glucuronidation
CYP450 interaction	Parent drug induces CYPs 3A, 2B, 2C, 2E and glucuronyl transferases	Weak inducer of CYP3A4 at doses ≥900 mg/d OXB MHD inhibits CYP2C9 at K_I >1,350 mol/L (minor) MHD inhibits CYP2C19 at K_I: 88 mol/L (minor)	Weak inducer of CYP3A4 at doses ≥800 mg/d Minor inhibition of CYP2C19
Differences in side effects	↑ Hematologic ↑ Dermatologic adverse effects	↑ Hyponatremia	Unknown at present

Abbreviations: K_I, binding affinity (lower numbers indicate stronger binding affinity); OXB, Oxcarbazepine.
NOTE. Tegretol and Trileptal are from Novartis Pharmaceuticals Corp (East Hanover, NJ), and Aptiom is from Sunovion Pharmaceuticals Inc (Marlborough, MA).

understanding of what most influences the side effect profile of these medications.

Evidence for Pain

Carbamazepine is approved for the use in trigeminal neuralgia and is currently the drug of choice for this condition.[33,46] Although this is the only true Food and Drug Administration indication for pain, there is some evidence to support benefit when used for tabetic lightning pains, postsympathectomy neuralgia, diabetic neuropathy, glossopharyngeal neuralgia, and phantom limb pain.[19,20,33,53,55,57] Oxcarbazepine does not carry a Food and Drug Administration-approved indication for trigeminal neuralgia. However, the American Academy of Neurology (AAN) guidelines for trigeminal neuralgia recommend oxcarbazepine as a reasonable first-line option.[33] Furthermore, available evidence suggests efficacy with oxcarbazepine for trigeminal neuralgia that may align with that of carbamazepine.[71] Benefit for allodynia, diabetic neuropathy, paroxysmal symptoms in MS, and peripheral neuropathy has also been recognized.[7,13,15,40,53,59,66] Case reports are available endorsing its use in postherpetic neuralgia refractory to gabapentin, regional complex pain syndrome refractory to gabapentin, and radiculopathy refractory to gabapentin.[12,14]

Beyond current evidence in pain, recent studies have shown that patients with a specific pain phenotype may experience maximum benefit from treatment with oxcarbazepine.[36] In a study evaluating response to oxcarbazepine, the interphenotype categorized as "irritable nociceptor" responded better to oxcarbazepine for total pain as well as for deep aching pain, lancinating pain, and pressure-evoked pain than the nonirritable nociceptor type. There was also a greater reduction in pain-related sleep disturbances.[36] Similarly, a recent study evaluated the effect of carbamazepine on 2 patients with inherited erythromelalgia, specifically with S241T mutation in the Nav 1.7 sodium channel.[30] Carbamazepine was found to reduce warmth-induced hyperactivity in dorsal root ganglia neurons in these patients as expected by previous genomic analysis. Patients also reported reduction in pain scores. These studies are encouraging and should catalyze interest for additional research in the area of genomic-guided pain management.[30] Please see Table 2 for studied doses and level of evidence.

Table 2. Evidence for Pain Efficacy in Commonly Prescribed Sodium Channel Blockers

Pain Syndrome	*Carbamazepine*	*Oxcarbazepine*	*Eslicarbazepine*	*GRADE Level of Evidence**
Tabetic lightning pains	800 mg/d[19]			Low
Trigeminal neuralgia	200 to 1,200 mg/d[33]			High
		1,200 to 2,400 mg/d[7,15,25,46,71]		Moderate
			(MS with refractory trigeminal neuralgia) 400 mg/d[29]	Low
Postsympathectomy neuralgia	600 mg/d[55]			Low
Diabetic neuropathy	200 to 600 mg/d (often requires >600 mg/d)[57]			Moderate
		150 to 1,200 mg/d (often requires >600 mg/d; average dose ~800 mg/d)[13]		Low
Glossopharyngeal neuralgia	400 to 800 mg/d[20]			Low
Phantom limb pain	800 mg/d[53]			Low
Spinal cord injury with allodynia		900 mg/d[40]		Low
Postherpetic neuralgia		(refractory to carbamazepine and gabapentin) 900 mg/d[17]		Low
Paroxysmal pain symptoms		1,000 mg/d[59]		Low
Complex regional pain syndrome		(refractory to gabapentin) 150 to 2,000 mg/d[56]		Low
Radiculopathy		(Refractory to gabapentin) 150 to 900 mg/d[66]		Low

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.
*GRADE classification for level of evidence.

Eslicarbazepine was approved for use in the United States in 2015; therefore, few studies for pain have been conducted. However, there are data to support its use in MS with refractory trigeminal neuralgia.[29]

Discussion

At this time, a primary focus of clinical practice is minimizing and decreasing reliance on opioid therapy, which is a significant change for many patients, and one many will not tolerate without effective alternatives to address their pain. There is increased emphasis on finding appropriate adjunct or alternative therapies that are effective but not habit-forming. Current treatment guidelines for neuropathic pain recommend the gabapentinoids (gabapentin and pregabalin) as first-line medications with strong evidence for pain, however, sodium channel inhibitors are currently considered a second-line option for neuropathic pain along with many other medications.[27] Many providers have questioned the utility of carbamazepine or oxcarbazepine for pain on the basis of the lack of endorsement from the AAN guidelines for diabetic peripheral neuropathy; however, this should be balanced against a more recent meta-analysis (2015) of neuropathic pain by the International Association for the Study of Pain.[27] In that meta-analysis, they suggest oxcarbazepine may have a specialized role because of trial results suggesting that oxcarbazepine might be significantly more effective in subgroups of patients with specific phenotypic expression.[9,27]

Among the 3 trials referenced by AAN, reduction in pain scores was observed in patients treated with doses >1,200 mg/d of oxcarbazepine.[9] Although there is not currently enough evidence to support a dose-dependent effect, trends in available evidence would suggest that benefit with oxcarbazepine for peripheral neuropathy is mostly observed at doses of >900 mg/d. Although the disparity between study quantity and quality supporting use for various pain conditions between first- and second-line medications is profound, emerging literature continues to highlight the potential uses of sodium channel inhibitors for pain management, which remains underappreciated.[27]

Although there is a lack of literature to guide the use of Navs in neuropathic pain compared with gabapentinoids, most literature evaluating the use of these agents for pain is in neuropathic pain syndromes. Notably, many Navs have been linked to neuropathic pain transmission.[54,67] However, some have been linked also to inflammatory pain, showing that prostaglandins enhance the activity of Nav 1.9 and Nav 1.7.[54,65,67] Because nonsteroidal anti-inflammatory drug (NSAID) agents block the formation of prostaglandins, it is not suggested that Navs replace NSAIDs for inflammatory pain. However, the pharmacology suggests that in patients unable to tolerate NSAIDs because of gastrointestinal or cardiovascular complications, a trial of sodium channel inhibitors may be effective. Clinical trials are needed to fully evaluate and characterize the targeted use of Nav blockers and place in therapy for inflammatory pain.

An area that has yet to be elucidated and may play a significant role in the development of medications for chronic pain management is targeting specific voltage gated sodium channel subtypes. Investigators are cur-

rently attempting to design drugs that selectively inhibit specific Navs; however, this may prove to be difficult because of the channel structural similarities. In lieu of pending new drug approvals for specific sodium channel inhibitors, perhaps clinicians should reconsider use of carbamazepine and oxcarbazepine.

Carbamazepine use has historically been limited because of undesirable pharmacokinetics and adverse effect profiles and oxcarbazepine use decreased by association and assumption of similar effects. Research has validated oxcarbazepine's improved pharmacokinetic and adverse effect profile compared with carbamazepine but interest in additional research into pain conditions has not been emphasized. The arrival of eslicarbazepine has generated new and promising evidence for sodium channel blockers as a class. Identification of sodium channel subtypes and their connection to pain etiologies justifies additional research for application into clinical practice.

Conclusion

The global effort to minimize and decrease reliance on opioid therapy is complicated by availability of effective treatment alternatives. There is significant disparity in the evidence gap between first- and second-line neuropathic pain medications that needs to be addressed through further research into specific pain conditions. In addition, targeting musculoskeletal and neuroinflammatory disorders with sodium channel inhibitors may be a new frontier in pain research. Identification of sodium channel subtypes with links to specific pain conditions and the ability to target them hints at the potential for truly individualized therapy and the necessary transformation of pain care. Sodium channel inhibitors are underutilized on the basis of available evidence, and emerging research has identified this area as promising for additional clinical trials to better guide clinical practice.

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