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The Management of Neuropathic Pain With a Focus Upon Older Adults

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By the year 2030, it is projected that the US population over the age of 65 years will be 70 million (one-fifth of the US population). Pain of various etiologies initiates about 50% of yearly physician visits and is the most frequent reason for health care consultation in the United States identified commonly by the older patient. The negative impact on the patient coupled with less than optimal treatments often presented to the patient elicit patient and prescriber frustration with inadequate outcomes. This article is focused at pharmacotherapeutic selections to be utilized in a polymodal fashion for the older adult presenting with neuropathic pain. The pharmacotherapies are to be titrated in a patient-specific patient centered–patient focused–personalized pharmacotherapeutic care. The classes of agents discussed include antidepressants, mood stabilizers/antiseizure agents, opioids, anesthetics, and miscellaneous agents.

Keywords: neuropathic pain, elderly, antidepressants, opioids, antiseizure agents, anesthetics, patient-specific treatment, patient focused, personalized pharmacotherapeutic care

INTRODUCTION

By the year 2030, the population of those aged 65 years or older is projected to reach 70 million (20% of the US population).[1] The chronic conditions associated with older adults—such as osteoarthritis, atherosclerosis, cancer, and diabetes—are likely to contribute to the already escalating costs of health care. The current annual spending on older adults is approximately $300 billion—close to one-third of the total US health care costs.

Pain of any etiology causes half of all yearly visits to a physician; consequently, pain is the single most frequent reason for health care consultation in the United States.[2,3] Among elderly patients, pain is the most common symptom noted when consulting a physician.[4] A study of 97 residents of long-term care facilities found the most frequently reported sources of pain to be lower back pain (40%), arthritis (24%), previous fractures (14%), and neuropathies (11%).[5]

Neuropathic pain (NP) is a broad, descriptive term for a group of chronic pain syndromes as clinical consequences that are initiated or caused by a primary lesion or dysfunction in the nervous system physiology.[1] Unlike nociceptive pain syndromes, such as postoperative pain and arthritis, NP syndromes are not initiated by acute inflammatory cascade of events and must be managed differently with polymodal mechanisms.[4] For example, nonsteroidal anti-inflammatory drugs (NSAIDs) have little or no role in the management of NP.[5,6] Effective management of NP requires a mechanism approach coupled with chronic disease management approach with reliance on skillful use of adjuvant analgesics and judicious prescription of long-term opioids. Like all chronic syndromes (maldynia), NP is a multifaceted concept with biologic, psychologic, and social components.[7] Comprehensive management must exceed that of mere pain relief in an

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attempt to understand and support the patient in relation to his or her illness. This process entails patient-specific, patient-focused, and patient-centered personalized care.

Despite the prevalence and suffering precipitated by pain, it often remains as underreported and undertreated—especially in the elderly. Studies reveal that the incidence of undertreated pain ranges from 25% to 50% in adult communities,[2,3] from 45% to 80% in nursing homes,[3,5,8] and as high as 85% in long-term care facilities.[7] Older adults often opine that pain is inevitable and that the treatment is worse than the symptom. They fear underlying causes such as cancer, addiction, and the side effects of the analgesics. Health care providers lack adequate education in pain management, and some believe, mistakenly, that older patients have a higher pain tolerance. Because cures are not available for many chronic conditions that manifest in older adults, there must be a clear focus on multidisciplinary comprehensive management of the pain associated with these conditions.

Published treatment guidelines for the assessment, treatment, and monitoring of chronic pain in elderly patients—including guidelines from the American Geriatrics Society and American Medical Directors Association [9,10]—advocate individualized pain management. This is particularly important for patients with multiple underlying chronic diseases. The American Medical Directors Association guidelines state:

> "In the long-term care setting, the comfort and well being of the individual patient must be paramount. This principle is the foundation for effective management of chronic pain. Neither resource constraints nor the perception of social disapproval . . . must ever be an excuse for inadequate pain control."[10]

NEUROPHYSIOLOGY OF AGING

Many functional, structural, and biochemical changes have been documented in elderly subjects.[11] For example, both unmyelinated and myelinated peripheral nerves decrease with age, and researchers have observed a marked increase in the number of sensory fibers with signs of damage or degeneration as age advances.[12–15] The effects of age on the human brain are known to be extensive, involving substantial changes in structure, neurochemistry, and function. Widespread degenerative changes have been found in spinal dorsal horn sensory neurons of healthy older adults,[16] and there is strong evidence of a progressive, age-related loss of serotonergic and noradrenergic neurons in the dorsal horn[17,18] suggesting impairment of the pain inhibitory system.

The pain threshold, that is, the minimal stimulus that is sensed as noxious,[19,20] has been used as a measure for investigating aging and pain function. An increased pain threshold has been shown with age, and decreased acuity for pain may place older people at a greater risk of tissue damage coupled with a reluctance to report pain. However, aging does not seem to be associated with substantive functional change over much of the pain stimulus–response curve. With pain that is persistent, older patients are especially vulnerable to the negative impacts of pain. Comprehensive discussions of the elderly and pain are published elsewhere focusing on nociceptive and geriatric pathophysiology.[8,19,21]

DIAGNOSIS AND ASSESSMENT

In general, the diagnostic challenge of NP remains in disconnecting the stimuli from the symptoms. The more common form—nociceptive pain (eudynia)—is usually localized and subsides as healing occurs or when the causative stimulus is removed. NP is more elusive, and the lesions arise in all neuraxis levels, often manifesting with negative neurosensory symptoms, such as loss of sensation, or with positive sensory phenomena symptoms such as paresthesia, hyperalgesia, dyesthesia, or allodynia. A diagnosis of NP is easily missed if the provider fails to recognize the signs and symptoms of neural dysfunction. On the other hand, there is the risk of misdiagnosing patients as having only NP when nerve damage and coincidental pain arise from another source.

In addition to a comprehensive medical, surgical, psychiatric, social laboratory, history, and review of systems, a diagnostic workup for NP must include a comprehensive physical and neurologic examination. The medical history is valuable in identifying the onset, location, and distribution of the pain, which is generally consistent with the degree of the neural lesion or the extent of the trauma. The quality of the pain should be assessed using patient-specific pain scales or other quantifiable descriptors. Although there is considerable overlap between nociceptive pain and NP in terms of patient symptoms, the symptoms that are more suggestive of NP include descriptions of continuous burning; electrical sensations; and other abnormal sensations (as seen with chronic dysesthesias) or sharp, stabbing, shooting, knifelike pains, electric shock, numbness, pins/needles often with a sudden paroxysmal pattern.

Pain descriptors vary among the NP syndromes, for example, patients with postherpetic neuralgia (PHN) often identify their pain as being sharper, less cold,

more sensitive, and itchier than pain identified by patients with diabetic peripheral neuropathy (DPN), peripheral nerve injury, or reflex sympathetic dystrophy. These data support the suggestion that NP is a collection of syndromes with different neuropathic processes.[22]

A thorough general physical/neurologic examination is critical because the diagnosis of NP relies on demonstrating sensory abnormalities in the area innervated by the damaged nerve. Instruments that can be used for assessment include warm and cold objects to test for temperature sensation, a camel hairbrush or cotton swab to detect touch or allodynia, and a pin to detect pain sensation.

Commonly used tools for measuring pain, for example, the visual analog scale, the McGill Pain Questionnaire, and the Verbal Descriptor Scales, are reliable and valid measures of pain intensity and unpleasantness. However, they are not adequate for the domains affected by NP. There are 2 scales developed specifically to assess distinct pain qualities associated with NP:

- *Neuropathic Pain Scale*[23]*:* This includes 2 items that assess the global dimensions of pain intensity and pain unpleasantness and 8 items that assess specific qualities of NP. An 11th item assesses the temporal sequence of pain.
- *Leeds Assessment of Neuropathic Symptoms and Signs*[24] *Pain Scale:* This is a 7-point scale based on an analysis of sensory description and bedside examination of sensory dysfunction. An advantage of using the Leeds Assessment of Neuropathic Symptoms and Signs is that it provides immediate information in clinical settings.

Psychological factors also must be assessed. Factors such as mood, physical functioning, pain-coping strategies, and social support can have a significant impact on both the patient's ability to adjust to NP and the effectiveness of treatment. Depression has been associated with the pain of PHN, spinal cord injury, and human immunodeficiency virus (HIV) disease. Similarly, specific pain-coping strategies predict pain severity, psychological distress, and physical function. A number of psychological assessment tools are available, including the Beck Depression Inventory,[24] the Pain Disability Index,[25] the Coping Strategies Questionnaire,[26] and the Multidimensional Pain Inventory.[27]

In the older adult, the initial assessment for NP may be complicated by factors such as incomplete medical records, incomplete disclosure of alcohol or recreational drug use history, lack of appropriate diagnostic tests, and undisclosed pharmacotherapies. A high incidence of vision, hearing, and cognitive impairments in the elderly also contribute to the difficulty in assessment. However, patients with moderate cognitive impairment can provide useful and reliable information if the provider is patient and allows adequate time. Concrete questions with ''yes'' or ''no'' responses are helpful. By observing patient behavior and obtaining information from family or other caregivers, one can obtain valuable sources of information when the patient lacks optimal communication skills. Unlike a younger population, aggressive testing for a definitive diagnosis or implementation of complicated treatment protocols is less important than providing comfort, maintaining cognitive function, and effective symptom management, especially near the end of life.[28]

PHARMACOLOGICAL MANAGEMENT

Pharmacotherapy choices with age-related modifications in the older adult are much the same as those for younger adults, with a few exceptions, which will be elucidated in the discussion that follows. The pharmacologic management of NP is essentially the same despite the etiology. In general, literature-based evidence is insufficient; clinicians often select a therapy or combination of therapies that have demonstrated benefit in NP whether the evidence is literature based or is from anecdotal evidence. As noted in the American Geriatrics Society clinical practice guidelines on persistent pain in older adults, often a combination of medications with complementary mechanisms (polymodal/multimodal) of action may provide greater therapeutic benefit with fewer side effects than provided by higher doses of a solitary agent.[29] Antidepressants, antiseizure medications, tramadol, selected opioids, and selected topical agents are generally considered first line. Selected muscle relaxants and selected miscellaneous agents (eg, clonidine) may be used in cases that are more difficult to treat.

As noted, evidence for the long-term (over years) use of medications for chronic pain symptoms is generally lacking, and evidence specific to older adults is even sparser. Most studies are not comparable with realistic clinical scenarios for multiple reasons: Studies are typically of a short term (days to months) and typically only allow the use of a single agent for pain management. Additionally, the trials often do not address which symptoms respond and which do not respond to treatment; outcome measures vary, and most trials report a strong placebo response.

Consequently, comparisons among trials and their clinical application are difficult.[30]

GENERAL CONSIDERATIONS

The choice of initial medication selection should include the consideration of current medical and/or psychosocial comorbidities, including affective disorders and insomnia; potential drug-disease and drug–drug interactions including current and historical prescription, nonprescription, and vitamins/phytopharmaceuticals; the anticipated side effect profile of the new medication and anticipated patient adherence acceptance; ease of dose administration, the willingness/ability of the patient to endure a possible lengthy dose titration schedule; and imposed financial burden.

A discussion/verbal agreement between the provider and the patient/caregiver(s) should occur before the initiation of medication therapy. This should include the identification of target symptoms and target functions and ensure that the patient and/or their caregiver(s) have realistic goals and expectations of therapy. It is often helpful to remind the patient that medications cannot usually eliminate the pain or the etiology of the pain; the intent is to decrease the pain in quality and intensity of the painful symptoms. Based upon the findings in the literature and experience, pain medications in general, typically reduce pain by approximately 30% in any given individual. Obviously, one attempts to use modalities to improve upon that figure but is often limited by side effects and the ability of the available agents to target the symptom(s).

Frequent follow-up, encouraged in the titration stages either by office visit or by telephone is recommended and in the progressive treatment phase.[31] To assist with medication adherence and compliance and thus with improving outcomes, patients, and/or their caregivers, should be involved in the decision-making process throughout the medication selection and follow-up assessment periods. Although it may prolong the course of treatment, conservative changes to the medication regimen, changing only one drug at a time, and providing a conservative dose titration schedule, will help ensure the lowest effective dose with the fewest number of medications to minimize the potential for adverse drug effects and unnecessary polypharmacy. However, in general, the treatment of NP often involves a combination of medications, initiating each medication in a sequential manner.

In NP, patients often report a constant baseline pain with episodes of either spontaneous or provoked shooting pain. Pain descriptors often include stabbing, throbbing, aching, squeezing, cramping, shooting, freezing, burning, or stinging.[30] Patients may describe numbness, or periods of ''pins and needles'' or tingling sensations. The affected area may exhibit allodynia (pain to a typically nonpainful stimulus) and/or hyperalgesia (pain that is out of proportion to the stimulus). It is postulated that the antidepressants seem to show benefit for burning pain, and antiseizure medications may provide benefit for the shooting, lancinating pain, although this has not been verified by controlled trials.[30] Numbness, especially in the older adult, may potentiate the possibility of gait abnormalities, falls, and wound care issues.

Acetaminophen and NSAIDs may be beneficial in certain types of NP syndromes that involve an ongoing inflammatory component, such as reflex sympathetic dystrophy (also known as chronic regional pain syndrome) or certain types of chronic demyelinating neuropathies. But in general, there is limited evidence to support the use of NSAIDs in NP.[32]

First-line medications identified by The International Association for the Study of Pain (IASP) consensus treatment recommendations panel are listed in Table 1.[31] Options for medication management will be discussed by drug class.

ANTIDEPRESSANTS

Tricyclic antidepressants—tertiary and secondary amines

Tricyclic antidepressants (TCAs) have been the most studied and seem to show the most consistent benefit in placebo controlled trials of PHN and DPN. Approximately 40%–60% of patients achieved at least a partial response to the TCAs.[31] However, based on 1 review, the total number of patients in all published studies of TCAs in DPN totaled <200 patients and showed only modest benefit when compared with placebo.[33] In studies using TCAs in other types of NP (HIV neuropathy, spinal cord injury, cisplatin-induced neuropathy, phantom limb pain, cancer-associated neuropathy, lumbar root pain), TCAs and placebo showed similar responses.[31] Despite this, TCAs are often considered a first-line choice for the treatment of NP symptoms. They should, however, be used with a high degree of caution, if at all, in any older adults.

The mechanism for analgesia is not fully identified, but several theories exist. It is believed that the combination of norepinephrine (NE) and serotonin (5HT) reuptake inhibition (which in turn inhibits nociceptive pain pathways) is at least partially responsible.[34] TCAs also seem to block sodium channels,[30,32] with a theoretical anesthetic mechanism and with

Table 1. IASP first-line medication options for the treatment of neuropathic pain symptoms.

Medication	Typical side effects	Considerations
TCA Nortriptyline or despiramine	Anticholinergic effects Cognitive changes Weight gain Orthostasis Potential for cardiotoxicity (QTc prolongation)	Hepatic failure, cardiac disease, prostate enlargement, glaucoma Avoid if recent MI, second or third degree heart block Consider pretreatment ECG Suicide risk Serotonergic—monitor for serotonin syndrome May increase fall risk Withdrawal effects if abrupt discontinuation Blood levels increased by most SSRIs Can draw blood levels to monitor for toxicity (not for analgesia); avoid in older patient
SNRI Duloxetine Venlafaxine	Nausea, dyspepsia, diarrhea Drowsiness or may be activating	Hepatic failure, renal insufficiency, hypertension Serotonergic—monitor for serotonin syndrome Withdrawal effects if abrupt discontinuation
$\alpha 2\delta$ Ligands Calcium channel $\alpha 2\delta$ ligands Gabapentin Pregabalin	Drowsiness, dizziness, peripheral edema, weight gain	Renal insufficiency
Topical lidocaine (patch 5%)	Local skin reactions, rash	Use only on intact skin Avoid overuse in patients with hepatic insufficiency Use with caution, if at all, in patients taking class I antiarrhythmics
Opioids* Morphine Oxycodone Methadone Levorphanol	Drowsiness, dizziness, constipation, nausea, vomiting, gastroparesis, mental status changes	Morphine—with caution in renal insufficiency Methadone—recommend use only by providers experienced in using this agent—long half life; QT prolongation In general, consider history of substance abuse, suicide risk, potential drug interactions; oxycodone abuse liability
Tramadol	Drowsiness, dizziness, nausea, vomiting, constipation, seizure risk	Serotonergic—monitor for serotonin syndrome Multiple potential drug interactions Risk of dose-related seizures—see text

*First line only in selected circumstances, see text.

chronic use seem to decrease gamma-aminobutyric acid type b (GABA-b) and *N*-methyl-D-aspartate (NMDA) glutamate receptors[35] both of which seem to be involved in the pathology of NP.

The onset of pain relief with the TCAs may be as soon as 3–10 days[34] but in some patients may take as long as several weeks. Analgesic doses are generally lower than antidepressant doses are, and the effects on pain symptoms seem to be independent of the effects on depression.[32,34] In situations in which TCAs are used in older adults, the dose should be initiated at 10 mg/d (the same for all TCAs) and titrated slowly to either effect or to tolerability. Doses similar to those used in younger adults may be required. It may be

Table 2. Selected cytochrome P450 substrates, inducers, inhibitors.

Isoenzyme system	Substrate	Induced by	Inhibited by
1A2	Betaxolol, caffeine, clomipramine, clozapine, cyclobenzaprine, doxepin, duloxetine, estrogens, flutamide, fluvoxamine, mexiletine, mirtazapine, propranolol, riluzole, ropinirole, theophylline, thiothixene, trifluoperazine	Carbamazepine, phenobarbital, primidone, rifampin	Amlodipine, caffeine, cimetidine, ciprofloxacin, diclofenac, fluoxetine, fluvoxamine, gemfibrozil, ketoconazole, lidocaine, mexiletine, nifedipine, norfloxacin, ofloxacin, propofol, tranylcypromine, zileuton
2B6	Bupropion, cyclophosphamide, efavirenz, irinotecan, ketamine, promethazine, propofol, selegiline	Carbamazepine, nevirapine, phenobarbital, phenytoin, primidone, rifampin	Desipramine, doxorubicin, paroxetine, sertraline
2C8	Amiodarone, paclitaxel, pioglitazone, repaglinide, rosiglitazone, tretinoin	Carbamazepine, phenobarbital, phenytoin, primidone, rifampin	Atazanavir, celecoxib, felodipine, fenofibrate, gemfibrozil, irbesartan, losartan, pioglitazone, quinine, rabeprazole, ritonavir, rosiglitazone, tamoxifen, trimethoprim
2C9	Alosetron, bosentan, carvedilol, celecoxib, dap sone, fluoxetine, glimepiride, glipizide, ketamine, losartan, montelukast, nateglinide, paclitaxel, phenytoin, propofol, sulfadiazine, sulfamethoxazole, sulfinpyrazone, sufisoxazole, tamoxifen, torsemide, trimethoprim, voriconazole, warfarin, zafirlukast, zopiclone	Carbamazepine, phenobarbital, phenytoin, primidone, rifampin	Amiodarone, delavirdine, fenofibrate, flucona zole, flurbiprofen, fluvastatin, gemfibrozil, ibuprofen, indomethacin, irbesartan, ketoconazole, losartan, mefanamic acid, nicardipine, omeprazole, pantoprazole, piroxicam, quinine, sulfadiazine, sulfamethoxazole, sulfinpyrazone, sulfisoxazole, trimethoprim, warfarin, zafirlukast
2C19	Carisoprodol, cilostazol, citalopram, clomipr amine, diazepam, escitalopram, esomeprazole, imipramine, lansoprazole, methsuximide, nelfinavir, omeprazole, pantoprazole, pentamidine, phenobarbital, phenytoin, progesterone, rabeprazole, sertraline, trimipramine, voriconazole	Carbamazepine, phenytoin, rifampin	Cimetidine, delavirdine, fluconazole, fluoxetine, fluvoxamine, gemfibrozil, isoniazid, ketoconazole, loratadine, modafinil, nicardipine, omeprazole, propofol, rabeprazole, sertraline, tranylcypromine
2D6	Amitriptyline, amoxapine, aripiprazole, atomox etine, betaxolol, captopril, carvedilol, chloroquine, chlorpromazine, clomipramine, codeine, desipramine, dextroamphetamine, dextromethorphan, doxepin, doxorubicin, duloxetine, flecainide, fluoxetine, fluphenazine, fluvoxamine, haloperidol, hydrocodone, imipramine, labetalol, lidocaine, lomustine, maprotiline, methamphetamine, methylphenidate, metoprolol, mexiletine, mirtazapine, nefazodone, nortriptyline, oxycodone, paroxetine, perphenazine, pindolol, procainamide, promethazine, propafenone, propranolol, protriptyline, risperidone, sertraline, tamoxifen, tamsulosin, thioridazine, timolol, tolterodine, tramadol, trimipramine, venlafaxine		Amiodarone, chloroquine, chlorpromazine, ci metidine, clomipramine, clozapine, cocaine, delavirdine, desipramine, diphenhydramine, duloxetine, erythromycin, fluoxetine, haloperidol, imipramine, isoniazid, ketoconazole, lidocaine, methadone, methimazole, nicardipine, paroxetine, pergolide, pioglitazone, quinidine, quinine, ritonavir, ropinirole, sertraline, thioridazine, tranylcypromine, trazodone

(continued on next page)

Table 2. *(Continued)* Selected cytochrome P450 substrates, inducers, inhibitors.

Isoenzyme system	Substrate	Induced by	Inhibited by
3A4	Albuterol, alfentanil, alprazolam, amiodarone, amlodipine, amprenavir, aprepitant, aripiprazole, atazanavir, atorvastatin, bisoprolol, bosentan, bromocriptine, budesonide, buprenorphine, buspirone, busulfan, carbamazepine, cerivastatin, chlordiazepoxide, chloroquine, chlorpheniramine, cilostazol, cisapride, citalopram, clarithromycin, clonazepam, clorazepate, cocaine, colchicine, cyclophosphamide, cyclosporine, dantrolene, dapsone, delavirdine, diazepam, dihydroergotamine, diltiazem, disopyramide, docetaxel, doxepin, doxorubicin, efavirenz, eletriptan, enalapril, eplenerone, ergots, erythromycin, escitalopram, estrogens, etoposide, felodipine, fentanyl, flurazepam, flutamide, haloperidol, ifosfamide, indinavir, irinotecan, isosorbide di- and, mononitrate, isradipine, itraconazole, ketamine, ketoconazole, lansoprazole, letrozole, lidocaine, losartan, lovastatin, progesterones, mefloquine, methadone, midazolam, mirtazapine, modafinil, montelukast, nateglinide, nefazodone, nelfinavir, nevirapine, nicardipine, nifedipine, nimodipine, nisoldipine, ondansetron, paclitaxel, pergolide, phencyclidine, pimozide, quetiapine, quinidine, rabeprazole, ranolazine, repaglinide, rifabutin, ritonavir, saquinavir, sibutramine, sildenafil, simvastatin, sirolimus, sufentanyl, tacrolimus, tamoxifen, tamsulosin, tetracycline, theophylline, tipranavir, tolterodine, trazodone, triazolam, trimethoprim, vardenafil, venlafaxine, verapamil, vinblastine, vincristine, vinorelbine, zolpidem, zonisamide, zopiclone	Carbamazepine, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin	Amiodarone, amprenavir, aprepitant, atazanavir, caffeine, cimetidine, clarithromycin, clotrimazole, cyclosporine, delavirdine, desipramine, diltiazem, doxycycline, erythromycin, fluconazole, grapefruit juice, haloperidol, indinavir, isoniazid, ketoconazole, lidocaine, metronidazole, nefazodone, nelfinavir, nicardipine, propofol, quinidine, ritonavir, saquinavir, sertraline, telithromycin, verapamil, voriconazole

How to use this table: The substrate drug is metabolized by the isoenzyme system noted in the table. Inducers of this isoenzyme increase the metabolism of the substrate; inhibitors of this isoenzyme decrease the metabolism of the substrate. Inducers effectively decrease blood levels, typically resulting in decreased benefit, whereas inhibitors effectively increase blood levels of the substrate medication, typically resulting in a higher potential for toxicity/adverse events. The exception is with codeine, hydrocodone, and oxycodone, all of which are metabolized to a more potent analgesic. The inhibition of metabolism typically reduces the pharmacologic effect, clinically seen more often with codeine than with hydrocodone or oxycodone.

useful to use TCA blood concentrations to monitor for toxicity, but there is no known correlation between drug concentration and analgesia.[34] Side effects precede any therapeutic response. The side effects, adverse and toxic effects, outweigh therapeutic outcomes.

TCAs are associated with multiple side effects and potential toxicities. The tertiary amines (amitriptyline, doxepin, clomipramine, imipramine) possess prominent anticholinergic properties and are more serotonergic and noradrenergic and thus associated with a higher incidence of dose-limiting side effects when compared with the more secondary amines; these agents should generally be avoided in older adults. Secondary amines (desipramine, nortriptyline) have more moderate anticholinergic properties and are potentially problematic in the older adult. Anticholinergic effects include drowsiness, constipation, urinary retention, changes in cognition, and dry mouth; they may also cause acute-angle closure glaucoma. The TCAs as a class possess alpha-1 ($\alpha 1$) antagonist properties (orthostasis, vasomotor rhinitis, sedation) and antihistamine (H_1, H_2) properties (sedation, weight gain). TCAs are also associated with cardiotoxicity (QT_C prolongation, heart block, arrhythmias)[32]; tachycardia may result from excessive anticholinergic effects. The literature suggests an increased risk of sudden cardiac death at TCA dosages of 100 mg/d or higher[31] and an increased rate of hip fractures in older adults taking nortriptyline.[32] Additionally, TCAs can be fatal in intentional, or unintentional, overdose situations. As a class, TCAs are affected by drug interactions involving the Cytochrome P450 system in the liver. As noted in Table 2,[36] many selective serotonin reuptake inhibitors (SSRIs) affect the 2D6 isoenzyme to inhibit the metabolism of many of the TCAs causing clinically significant increases in TCA blood levels. Both cyclobenzaprine (muscle relaxant) and carbamazepine (antiseizure) are structurally similar to TCAs; their concomitant use causes additive side effects.

Abrupt withdrawal should be avoided if possible; withdrawal symptoms may include restlessness, insomnia, muscle aches, headache, nausea, diarrhea, drowsiness, nightmares, irritability, and movement disorders.[34] Depending upon the dose and the duration of use, one should perform a slow taper, typically over 2–4 weeks[34]; however, if the dose is high or the duration is in years rather than in months, a slower titration, perhaps over several months should be used.

Use in older adults should be considered only after careful consideration of risks and benefits and when Food and Drug Administration (FDA)-approved drugs have failed. None of the TCAs have FDA approval for use in pain management.

Antidepressants (serotonin/norepinephrine dual reuptake inhibitors)

Both venlafaxine and duloxetine are serotonin–norepinephrine reuptake inhibitors (SNRIs) and are FDA approved for depression and anxiety; duloxetine is FDA approved additionally for use in DPN, fibromyalgia, and chronic musculoskeletal pain including discomfort from osteoarthritis and chronic lower back pain. Desvenlafaxine, the active metabolite of venlafaxine, is FDA approved for the treatment of depression. Milnacipran, an SNRI, is indicated for depression in Europe, and fibromyalgia in the United States and may be an option for selected patients with NP as it is more noradrenergic than serotonergic is. A PubMed and a MedLine search in June 2010 did not reveal any literature using desvenlafaxine in chronic pain management.

The analgesic mechanism of the SNRIs is presumed to be similar to that of the TCAs regarding the reuptake inhibition of NE and 5HT, but SNRIs are associated with fewer side effects and toxicities due to there being no therapeutic activity at the other receptors. According to the respective manufacturer's product information, duloxetine has minimal affinity for adrenergic, cholinergic, dopaminergic, histaminergic, opioid, GABA, or glutamate receptors, in vitro[37] and venlafaxine has minimal affinity for the alpha-1, muscarinic cholinergic, or H1 histaminergic receptors.[38]

Duloxetine inhibits in a balanced fashion the reuptake of 5HT and NE at low and therapeutic doses, whereas venlafaxine primarily inhibits 5HT reuptake at lower doses; the NE reuptake blocking properties are not evident until a dose of approximately 75–100 mg/d in younger adults. Randomized controlled trials (RCTs) of venlafaxine in DPN and other varying types of polyneuropathies seem to require dosages of 150–225 mg/d[31]; usage in PHN and certain other peripheral and central neuropathic conditions showed more inconsistent results, but in a recent review, it was noted that in some cases, the lack of benefit may be explained by the utilization of doses that may have been too low.[31] Beneficial effects are typically seen after 2–4 weeks at the target dose.[31] It should be noted that venlafaxine is available in both an immediate release formulation (2 or 3 times per day dosing) and an extended release formulation (1 or 2 times per day dosing).

Duloxetine and venlafaxine are relatively well tolerated and as with TCAs, side effects can be minimized if the dose is initiated at a lower dose (ie, 20 mg for duloxetine) and titrated upward on a weekly or biweekly basis. It seems that for NP, duloxetine 120 mg/d is no more effective than 60 mg/d and is associated with a higher incidence of dose-related

side effects.[31] Venlafaxine is associated with blood pressure elevations, though not in all patients; sometimes, it seems to be idiosyncratic and sometimes dose related; 1 RCT noted ECG changes in approximately 5% of patients.[31] Duloxetine is also associated with small increases in blood pressure but typically at the higher dosages. Duloxetine has been associated in a small percentage of patients with dose-related hepatotoxicity and should be avoided in patients with routine alcohol consumption, clinically significant liver disease with urinary retention and should be avoided or used with caution in patients with pre-existing symptoms.[37]

Duloxetine needs no alterations in dose or intervals when the creatinine clearance is 30–80 mL/min. Steady state is achieved in 3 days with an elimination half life of 12 hours (range: 8–17 hours). Metabolism is mediated by the CYP 450 1A2 and 2D6 pathways.

All of the SNRIs are associated with possible hyponatremia.

In general, duloxetine is considered a safer and more effective choice than the TCAs in older adults for the treatment of NP symptoms. Duloxetine is the only SNRI FDA approved for diabetic peripheral neuropathy. This FDA indication reinforces patient confidence in the agent throughout the titration period.

Other antidepressants

In general, the selective SSRIs are not effective in the symptom management of NP. Bupropion, a unique antidepressant that inhibits the reuptake of NE and dopamine, showed benefit in a small 6-week randomized, double blind, placebo controlled trial in nondepressed patients with NP.[39] The dose was initiated at 150 mg daily of the sustained release formulation for 1 week then increased to 150 mg twice daily for the remaining 5 weeks.[39] Bupropion lacks the anticholinergic, antihistaminergic, alpha blockade, and sexual dysfunction of many of the other agents. Side effects include dry mouth, headache, nausea, and insomnia; it can be more activating than other agents and is contraindicated in patients with seizure disorders.[30]

ANTISEIZURE MEDICATIONS

Calcium channel alpha-2 delta ligands

Gabapentin and pregabalin are both considered alpha-2 delta ($\alpha 2\delta$) ligands. Both bind to the $\alpha 2\delta$ subunit of the calcium channel and ultimately inhibit the release of glutamate (excitatory neurotransmitter), NE, and substance P.[31] Both are renally eliminated and have similar side effect profiles. The most common side effect is sedation, which may be beneficial in comorbid insomnia. Dizziness is also common and is a strong consideration when used in an older adult. Some older adults may also experience cognitive changes or gait impairment.[31] Slow dose titrations typically minimize the occurrence and severity of side effects. Both gabapentin and pregabalin are associated with peripheral edema (hands and feet) and weight gain. Pregabalin is associated with dry mouth, blurred vision, thrombocytopenia, and euphoria.[40] In premarketing trials, pregabalin was associated with creatine kinase elevations (1.5% vs. 0.7% placebo of 3 times the upper limit of normal), decreased platelet count (3% vs. 2% placebo for a clinically significant drop of 20% below baseline and $<150 \times 10^3/\mu L$), and a prolonged PR interval change on ECG (with mean change of 3–6 milliseconds at pregabalin doses $\geq$300 mg/d).[40]

When discontinuing, both medications should be tapered to off over at least 1 week, longer depending on the dose and duration of therapy. It can usually be tapered more quickly than it was initially titrated; abrupt withdrawal is reported to precipitate seizures in some individuals.

Gabapentin is FDA approved for the treatment of PHN and has demonstrated beneficial effects when compared with placebo in multiple different NP conditions. There are also trials showing lack of benefit, though few in number.[31] Because it is eliminated renally, it is safe to use in mild hepatic impairment but must be dose reduced in renal insufficiency. The manufacturer supplies a renal dosage guideline in their product information[41]; note that gabapentin is removed by hemodialysis.[41] Anecdotally, older adults typically respond to lower dosages and require a much more conservative titration than do younger adults. It is thought that in younger adults, the minimally effective dose for NP is approximately 1800 mg/d, with doses up to 3600 mg/d sometimes required. In older adults, renal function is compromised by virtue of age alone, so as a result, the minimally effective dose will likely be $<$1800 mg/d. Depending upon age and comorbidities, a typical conservative gabapentin titration might start at 100 mg/d (at bedtime) and increase by 100 mg/d every week until either pain benefit or bothersome side effects occur. The recommended manufacturer's titration for PHN is 300 mg on day 1, 600 mg on day 2, and 900 mg on day 3, then titrated up to 1800–3600 mg/d, all given in 3 divided doses.[41] Benefits are typically seen approximately 2 weeks after the target dose is reached.[31]

Gabapentin displays absorption saturation kinetics. Once ingested, the drug relies on a carrier molecule in the intestinal tract for systemic absorption; the same molecule may also be responsible for the transport of gabapentin at various tissue sites.[42] The carrier molecule may be available in insufficient supply to

handle very high doses of gabapentin, with the excess gabapentin being eliminated before absorption. Of note, if given in 3 doses per day, only 60% of 900 mg/d, 47% of 1200 mg/d, 34% of 2400 mg/d, and 33% of 3600 mg/d is systemically absorbed.[41] Gabapentin is often dosed 3 times a day, but anecdotally, it seems that absorption and thus analgesia may improve if dosed 4 times per day instead.

The package insert for gabapentin indicates that the coadministration of gabapentin with hydrocodone, morphine, or naproxen all have been noted to increase gabapentin absorption and consequently, increase gabapentin blood concentration.[41] Aluminum/magnesium hydroxide antacids given with gabapentin decreased gabapentin absorption by approximately 20%; therefore, gabapentin should be dosed 2 hours after antacids are given.[41] It is unknown whether this is clinically significant.

Pregabalin is similar to gabapentin. Pregabalin is also more costly, was not available generically at the time of this writing, and is classed as a Schedule V Controlled Substance due to it causing profound euphoria. It is FDA approved for use in PHN, DPN, and fibromyalgia in addition to seizure control. It has shown benefit in 1 RCT in patients with NP associated with spinal cord injury.[31] None of the clinical trials discriminated euphoria from analgesia.

Pregabalin does not display absorption saturation kinetics and can be titrated more quickly than gabapentin. It can be dosed either twice a day (BID) or TID; the manufacturer recommends initial dosing of 150 mg/d (given TID) and titrated to 300 mg/d after 1 week in DPN and PHN, with a maximum dose of 300 mg/d in DPN and 600 mg/d in PHN (if no benefit is obtained after 2–4 weeks).[40] As with gabapentin, the manufacturer supplies a table in the product information for renally based dosing.[40] It is suggested that the dose be titrated more conservatively in older adults, some use 75 mg at bedtime to start,[31] others as low as 50 mg at bedtime (or less for more compromised renal function) with a dose titration every 5–7 days. A high degree of caution and patient monitoring is needed when beginning pregabalin in the older patient. One must remember to calculate creatinine clearance in all older patients and use their dose as a guideline on pregabalin/gabapentin.

Voltage-gated sodium channel inactivation

Medications in this class that have been used in NP syndromes include carbamazepine, lamotrigine (LMG), oxcarbazepine, phenytoin, topiramate (TOP), and valproic acid (VPA).[43] The mechanism for antiseizure activity seems to be the ability of these drugs to prolong the recovery time of specific sodium channels, which in turn delays the ability of the neuron to fire.[43] Evidence for the effectiveness of antiseizure medications for NP syndromes is limited and often inconsistent.[31]

Carbamazepine (generics)

Support for the use of carbamazepine (CBZ) is most consistent in the management of trigeminal neuralgia. It is a somewhat difficult medication to use for the following reasons: Oral absorption tends to be variable and may be delayed with higher doses compared with lower doses[43]; it has a narrow therapeutic index (difference between the therapeutic and toxic blood levels is narrow); it has an active metabolite (10,11-epoxycarbamazepine); it is associated with multiple potentially clinically significant drug interactions; it induces its own metabolism (autoinduction) so that higher doses may be required; it should be titrated slowly due to side effects and though uncommon is associated with hyponatremia, severe skin reactions, and various blood dyscrasias. Ongoing monitoring should include baseline and periodic CBZ blood levels, complete blood count, and liver function tests. Carbamazepine blood concentrations are intended to monitor for toxicity if suspected, rather than analgesia. Typical side effects include drowsiness, dizziness, lightheadedness, diplopia, and nystagmus. Less common side effects, but especially concerning in the older adult population, include cognitive impairment, agitation, restlessness, irritability, and the syndrome of inappropriate antidiuretic hormone secretion.[34] As noted earlier, CBZ is structurally similar to the TCAs (imipramine) and is therefore associated with side effects and precautions similar to the TCAs.[34]

The pharmacokinetics of CBZ are not linear; doubling the dose does not necessarily double the blood concentration or the effect. It is typically initiated at 50 mg twice a day and in younger adults may be increased slowly to approximately 1200 mg/d in 2–4 divided doses.[34] In older adults, one has to adjust the dose cautiously, using the lowest possible maintenance dose.

According to a review by Stacey,[32] CBZ seems to show effectiveness in trigeminal neuralgia and DPN but not in PHN or in central pain syndromes. Doses used in those studies ranged from 100 to 4000 mg/d.

Oxcarbazepine

Oxcarbazepine is similar to CBZ but is less studied for chronic pain management. Compared with CBZ, it is associated with fewer side effects and potential drug interactions (less potent enzyme inducer)[43] and does not induce its own metabolism. It too blocks the sodium channel but, in addition, seems to inhibit the

N-type and P-type calcium channels to decrease glutamate-mediated transmission.[30]

Oxcarbazepine is a prodrug; it has no activity on its own but is quickly converted to the active metabolite responsible for its activity.[43] It has however been associated with hyponatremia and severe skin reactions (Stevens–Johnson syndrome, toxic epidermal necrolysis); patients allergic to CBZ may also be allergic to oxcarbazepine.

Valproic acid

The discussion of VPA includes its derivative divalproex. The drug is FDA approved for the management of seizures, mania, and migraines. Chemically, divalproex is a compound comprising sodium valproate and valproic acid. In the gastrointestinal (GI) tract, valproic acid and divalproex dissociate to the valproate ion, the form required for absorption. If given in equivalent doses, all forms will provide equivalent quantities of the ion for absorption.[44]

In addition to its action on sodium channels, VPA also seems to decrease the electrical current at the T-type calcium channel. In vitro studies indicate that VPA increases GABA activity (to create an inhibitory effect) by stimulating the activity of glutamic acid decarboxylase (which is involved in GABA synthesis) and inhibiting GABA transaminase and succinic semialdehyde dehydrogenase (enzymes involved in the breakdown of GABA).[43]

Valproic acid and divalproex are available in multiple dosage forms, each with a slightly different absorption and dosing profile. Valproic acid is available as Depakene (and generically); divalproex is available as Depakote DR (delayed-release, 12-hour duration, BID dosing), Depakote ER (extended release, 24-hour duration, once daily dosing) and as Depakote sprinkles. Valproic acid is typically difficult to tolerate due to GI side effects and requires multiple daily dosing. Divalproex achieves more reliable absorption, is better tolerated, and may be dosed less often.

Regardless of the dosage form, VPA can be a difficult medication to use. It is highly protein bound, but because protein binding tends to be lower in certain situations (older adults, hepatic impairment, renal impairment, the presence of other highly protein bound drugs), the free (active) fraction is proportionally higher in these individuals.[44] VPA seems to rely on a carrier-mediated transport system for passage into and out of the cerebral spinal fluid[43]; it has at least 2 active metabolites,[43] is implicated in multiple potential drug interactions, and its kinetics are nonlinear.

Valproic acid and its derivatives contain a box warning in the manufacturer product information[44] regarding the association of hepatotoxicity (fatalities reported) and life-threatening pancreatitis. It is also associated with thrombocytopenia (dose related), inhibition of platelet aggregation, hyperammonemia with or without encephalopathy, and, more commonly, nausea vomiting, diarrhea, dyspepsia, somnolence, dizziness, asthenia, tremor, weight gain, and alopecia. The manufacturer recommends periodic complete blood count, liver function test, and VPA plasma concentrations (to monitor toxicity rather than effectiveness).[44]

The manufacturer's product information[44] reports a reduced clearance in older adults (by 39%) and increased free fraction (by 44%) compared with that in younger adults. Additionally, when studied against placebo in patients with dementia, the VPA group displayed somnolence and dehydration; some patients showed decreased nutritional intake and weight loss. Doses should be adjusted accordingly. Patients should be monitored for fluid/nutritional intake, dehydration, and drowsiness.[44]

The recommended starting dose in younger adults for migraine prophylaxis is 250 mg BID with titration up to 1000 mg BID. As previously noted, dosing for older adults when initiated should be lower and titrated more conservatively, if used at all.

Lamotrigine

In vitro studies show that LMG blocks sodium channels to stabilize the neuronal membrane and inhibits the release of the excitatory transmitter glutamate.[45] Short-term trials, case reports, and case series indicate that LMG showed benefit in phantom limb pain, NP associated with HIV, trigeminal neuralgia, poststroke pain, and DPN; doses in these reports ranged from 50 to 400 mg/d; not all literature, however, has been positive.[34]

Lamotrigine is associated with skin rashes that range from mild to serious, including but not limited to Stevens–Johnson and toxic epidermal necrolysis; skin conditions seem to be more common in children than in adults and more common with faster dose titrations. The manufacturer recommends a slow dosage titration to minimize the occurrence.[45] Overall, the dermatologic reactions are considered rare but may be serious if they do occur. Multiorgan failure, though rare, has also been reported. Lamotrigine should be used cautiously in renal insufficiency as the half life may be prolonged.[34] Other side effects include drowsiness, dizziness, blurred vision, nausea, vomiting, and difficulty with coordination.[45] It is implicated in several potential drug interactions, primarily with other

antiseizure medications.[45] It is not a first-line agent for NP and has not been well studied in the older adult population; therefore, caution should be exercised if it is considered in these individuals.

Topiramate

In addition to its sodium and calcium channel–blocking effects, TOP seems to enhance GABA activity at certain GABAa subtypes, inhibit glutamic acid, block activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-kainate subtype(s) of the glutamate receptor, and inhibit carbonic anhydrase.[46] Topiramate is eliminated renally and therefore requires a dose adjustment in older adults and in those with renal insufficiency. Topiramate is a CYP 450 3A4 inducer. It should also be dose adjusted in hepatic insufficiency, though the mechanism for this is unclear.[46] The most common side effects are drowsiness, dizziness, and nervousness, but unlike most other antiseizure medications that promote weight gain, TOP is associated with weight loss. Because it inhibits carbonic anhydrase, it is associated with nephrolithiasis (calcium phosphate stones) in rare situations and may cause a non–dose related hyperchloremic, nonanion gap metabolic acidosis (decreased serum bicarbonate), which generally occurs soon after TOP is started but can occur at any point during treatment.[46] Early symptoms may include fatigue, anorexia, and hyperventilation. Periodic laboratory monitoring is recommended in selected patients.[46] Acute myopia associated with secondary angle closure glaucoma has also been reported in patients taking TOP; early symptoms include eye pain and decreased visual acuity.[46] Enquire about this with each visit. Occurrence is typically within 1 month of drug initiation and should be discontinued if symptoms do occur.[46] Additionally, TOP may cause dose-related central nervous system changes that include confusion, psychomotor slowing, memory impairment, depression, and fatigue. These rare but potentially serious side effects, including central nervous system changes, may limit its use in older adults.

Topiramate doses, as for other medications, when started should be low and be titrated slowly; begin with 25 mg. If started too high or titrated too quickly, patients are more likely to experience agitation, anxiety, and word-finding difficulties.[47] Drowsiness is relatively common and not necessarily dose related.[47] Multiple daily doses (2–3 times a day) may be beneficial over that of augmenting a single dose.

A relatively recent review of topiramate in NP syndromes[47] indicates that topiramate may provide benefit, but the literature was limited, involved small numbers of patients, drop-out rates were as high as 55%, and the authors found only 2 prospective double-blinded RCTs. From this review, it seems that the minimum effective topiramate dose may be 50 mg/d, but it has been used at doses up to 600 mg/d; the authors report that there is insufficient literature to recommend a target dose. The onset of pain relief seemed to be 3–12 weeks.[47]

Topiramate is FDA approved for migraine prophylaxis, in addition to its seizure indications. In the nongeriatric population, the migraine dosage regimen is 25 mg at bedtime (HS) for 1 week, then 25 mg BID for 1 week, then 25 mg and 50 mg HS for 1 week, then 50 mg BID. Similar dosage regimens have been used to treat NP symptoms. Consider initiating 15-mg at bedtime in the older patient. Increase the dose by 15-mg every 3 days as tolerated.

Levetiracetam

A few published case reports cite the potential benefits of levetiracetam in NP syndromes.[32,48] It is an antiseizure medication with a yet-uncharacterized mechanism of action, although it seems to bind to a site on the intraneuronal vesicles, which are involved in exocytosis.[49] In vitro studies show that it also seems to partially inhibit N-type calcium channels and oppose negative modulators of GABA and glycine-regulated currents. It does not seem to affect sodium channels or T-type calcium channels or be directly associated with GABA or glutamate-mediated effects.[43,49]

Absorption is reliable and rapid; it is not bound to plasma proteins and is not involved in the Cytochrome P450 system,[43] making it a relatively easy medication to use. It is renally eliminated and therefore requires dose adjustment in older adults and in patients with renal insufficiency.[49] The most common side effects are drowsiness, dizziness, and weakness, but it has also been associated with an almost 15% occurrence of behavioral changes, which include aggression, agitation, anger, anxiety, depression, and irritability.[49] For this reason, it should be used cautiously in older adults.

TOPICAL MEDICATIONS

Topical capsaicin, lidocaine, and doxepin have been used in the treatment of NP. Topical capsaicin and lidocaine (5% patch) are FDA approved for use in the pain associated with *herpes zoster*; topical doxepin is FDA approved for the short-term use in management of itching associated with atopic dermatitis or lichen simplex chronicus.[50]

Topical lidocaine 5% patch

Lidocaine is a sodium channel blocker available in many dosage forms suitable for use in multiple conditions. Topical lidocaine (5% patch) is considered a first-line agent for localized NP. It may be initiated concurrently with an oral first-line agent as it may provide more immediate relief and has minimal systemic side effects. The 5% patch formulation has shown benefit in studies of PHN and in other NP conditions.[31,32] Systemic absorption is minimal if a maximum of 3 patches are used over 12 hours.[31] Alternate dosing strategies were studied in healthy, normal adults: 4 patches for 3 days (18 hours on and 6 hours off) or 4 patches for 3 days (changed either every 12 or every 24 hours) and was associated with low lidocaine plasma concentrations, which were well below those associated with adverse effects.[32] Anecdotally, the application of the patch for up to 24 hours has been used with benefit in one author's practice for ≥8 years; when the patch is removed after 12 hours approximately 95% of lidocaine remains in the patch. Prolonged use may enhance systemic absorption, cause localized skin irritation or may hasten tachyphylaxis to the drug. Postmarketing information includes reports of disorientation, confusion, somnolence, and dizziness, and though causality has not been confirmed, one may monitor for such effects if used in older adults.[51] Topical lidocaine should be used cautiously, if at all, in patients concurrently taking class I antiarrhythmics and in patients with severe hepatic impairment.[31]

One study showed benefit from the lidocaine gel formulation when used in PHN but not in patients with HIV neuropathy.[31] The gel is less expensive but may not provide a similar duration of benefit when compared with that provided by the patch. Anecdotally, lidocaine 5% ointment has also been used with benefit for localized NP; however, there may be systemic absorption concerns with the gel and the ointment formulations; one should consider the total body surface area being covered, the frequency of application, and whether or not the area will be occluded by clothing.

Topical capsaicin

Capsaicin is a compound derived from the hot chili pepper that stimulates and over time, desensitizes, the vanilloid receptor (VR1) (part of the transient receptor potential family of receptors) on sensory afferent neurons.[52] It causes the depletion of Substance P from type C nociceptive neurons.[32,52] Capsaicin has shown inconsistent results in the management of NP;[31,32] patients have difficulty tolerating the burning associated with application and are typically unable to complete an adequate trial. Capsaicin 0.025% and 0.075% cream are both available without a prescription; it should be used 3–4 times daily and may take several weeks of routine use to show benefits. The localized burning sensation at the application site typically subsides within several weeks of use and may be minimized with the use of oral NSAIDs.[30]

Topical tricyclic antidepressants

Doxepin, available as a topical cream (Zonalon and Prudoxin), is FDA approved for the use of pruritis in specific conditions. Limited studies are available, but it has also demonstrated benefit for the short-term use in nonspecific NP syndromes.[53] Frequent or excessive use, large body surface areas, occlusion, and skin integrity all affect the extent to which doxepin may be systemically absorbed with side effects consistent with those of the oral TCAs. Chronic use may also increase the risk of contact sensitization.

TRAMADOL

Tramadol is classified as an opioid medication but not a Drug Enforcement Administration controlled substance with a dual mechanism of action. However because it is a weak mu receptor agonist similar to dextromethorphan, the manufacturer's information indicates that it is a centrally acting synthetic opioid analgesic.[54] As with opioids, abuse potential exists. Both the parent drug (tramadol) and the active metabolite (*O*-desmethyl tramadol, otherwise known as M1) bind to the mu receptor; M1 also blocks the reuptake of NE and 5HT, similar to the TCAs and SNRIs. The M1 metabolite is a more potent analgesic than the parent is.[54] Tramadol may be chosen as an alternative to opioids; it typically provides weaker analgesia than the stronger opioids but with side effects similar to the opioids, including cognitive changes, constipation, dizziness, nausea, and orthostasis. In addition, tramadol is associated with the precipitation of seizures in patients with pre-existing seizure disorders and in the following seizure-naive patients: those taking other medications that decrease the seizure threshold, SSRIs, TCAs, opioids, monoamine oxidase inhibitors, and/or antipsychotics.[54] Additionally, tramadol is serotonergic and is implicated in causing serotonin syndrome in combination with other serotonergic medications (including but not limited to lithium, trazodone, SSRIs, SNRIs, St Johns Wort, TCAs, triptans, and Cytochrome P450 2D6 and 3A4 inhibitors).

Tramadol is shown to be beneficial in RCTs in various types of painful neuropathies, including PHN, DPN, postamputation pain, and various types of polyneuropathies with benefit noted after about 2–4 weeks of

use.[30,31] Tramadol should be used with caution in older adults, especially those over 75 years of age.[54] As with other medications, doses in older adults should start low and be titrated slowly typically with a maximum of 200 mg/d. Doses >300 mg/d have not demonstrated increased clinical benefit in populations of any age.[54] In addition, tramadol should be further dose adjusted in patients with renal and/or hepatic insufficiency.

OPIOIDS

Some opioids are considered second-line medications for the management of chronic NP by the IASP guidelines[31] and first line in other reviews,[32] illustrating the lack of agreement on the place of opioids in therapy. The IASP specifically indicates 4 situations in which opioids may be considered first line: during dose titration of a first-line medication, episodic severe pain exacerbations, acute NP, and neuropathic cancer pain.[31] Extrapolation from literature-based information is difficult. Studies using opioids for NP range in duration from 8 days to 8 weeks and often include multiple types of NP conditions and use multiple different opioids. From these studies, opioids are likely as beneficial as other medications used in the treatment of NP[31,32] but, in general, are associated with more side effects than TCAs and gabapentin are.

Eisenberg et al[55] performed a retrospective review and meta-analysis of opioid use in the treatment of nonmalignant NP. They included a total of 22 studies, 14 of which were considered short term (<24 hours) and used a crossover design, but in most cases, the opioid was administered intravenously (IV). The results were inconsistent: 6 trials showed benefit over placebo, and 5 trials showed efficacy equal to placebo. Two trials reported partial efficacy, and 1 trial reported benefit in the affective but not sensory component of pain. In the remaining 8 trials that were considered to be of an intermediate term (8–56 days, median of 28 days), 5 trials were crossover, and 3 trials were a parallel design; medications included morphine, oxycodone, methadone, and levorphanol. All 8 trials reported benefit from the opioid in decreasing spontaneous NP symptoms. The meta-analysis of 6 of these 8 trials indicated an average pain score improvement of 14 points out of 100 points when compared with placebo. Number needed to harm was calculated and reported as follows: nausea (3.6), constipation (4.6), drowsiness (5.3), vomiting (6.2), and dizziness (6.7); the authors reported that insufficient data were available for changes in cognition.[55]

The long-term safety of opioids is unknown; the chronic use of opioids is associated with hypogonadism immunonologic changes and the possible development of hyperalgesia. One must consider the possibility of addiction, diversion, or misuse when prescribing opioids,[31] even in the older adult population. In the older adult, cognitive changes and constipation are more common than in the younger adult, and dosing must be individualized to reflect age-related changes in renal and hepatic function. The IASP recommends the use of opioids for NP in patients who have failed or cannot tolerate the first-line agents or in those for whom first-line agents are not otherwise an option.[31]

TAPENTADOL

Tapentadol is a new compound with dual mechanisms of action. It acts centrally as an opioid analgesic on Mu receptors diminishing conduction of the ascending pathway transmission. At the same time, tapentadol enhances modulation on the descending noradrenergic pathways via reuptake inhibition also providing analgesia. The immediate release dosage peaks at 1.25 hours. There are no cardiovascular side effects with <1% reported having a change in heart rate at therapeutic doses.[56]

MUSCLE RELAXANTS

Evidence to support the use of muscle relaxants for NP is lacking.[32] In cases of spinal disorders or spasticity associated with upper motor neuron conditions, baclofen, dantrolene, and tizanidine have shown benefit.[32]

Baclofen has been used in trigeminal neuralgia and seems to work by inhibiting the release of excitatory neurotransmitters.[34] It should not be used in patients with a current condition or history of seizure disorders. Typical side effects include drowsiness, dizziness, nausea, vomiting, and confusion.[34] Baclofen is usually initiated at 5–10 mg BID or TID and increased by 5 or 10 mg every 2–3 days to a total of 50–60 mg/d, given in divided doses.[34] Dosing in older adults should be done conservatively and more slowly. Abrupt withdrawal should be avoided to minimize the chances of a withdrawal syndrome, which may include hallucinations, seizures, anxiety, and tachyarrhythmias up to 2 months after stopping the drug.[34] It has been suggested that if withdrawal symptoms do occur, one should resume the baclofen at the previous dose and decrease it by 5–10 mg/d on a weekly basis until it is tapered off.[34]

MISCELLANEOUS

Medications such as clonidine, mexiletine, and NMDA-receptor antagonists are generally agents reserved for use after failure or intolerance of medications with better effectiveness data.

Clonidine is thought to act by blocking the effects of NE on certain α receptors that may be associated with NP and may also increase GABAa activity.[34] Clonidine may be problematic in older adults as it may cause hypotension (or rebound hypertension if abruptly stopped), dizziness, drowsiness, and dry mouth. If used, dosing is typically initiated at 0.1 mg twice a day and increased by 0.1 mg/d on a weekly basis. The usual effective dose in a younger population is 0.3 mg twice daily.[34] Consider 0.05 mg cautious dosing increments in the older adults.

Mexiletine is an oral lidocaine-like medication typically used in the treatment of cardiac arrhythmias. Studies in DPN or other neuropathies show modest to no benefit.[30,31,33] It is poorly tolerated from a GI standpoint and should be dosed using blood levels to avoid toxicity. Other side effects include dizziness, tremor, irritability, nervousness, headache, and liver function abnormalities; it is contraindicated in patients with second or third degree heart block.[34]

NMDA-receptor antagonists include methadone, orphenadrine, amantadine, dextromethorphan (DM), ketamine, and memantine. Dextromethorphan is the *d*-isomer of the opioid methorphan (the *l*-isomer is levorphanol), but DM has no analgesic or addictive properties.[57] It has been studied for NP in a small number of patients for short periods of time with mixed results in 3 crossover RCTs.[58] Dextromethorphan doses are much higher for pain management than those used for cough suppression; The review of Wolfe[30] cites 1 small study in painful diabetic neuropathy that used a mean dose of 381 mg/d; the most prominent side effects were ataxia and drowsiness. Overall, memantine and DM have shown little to no benefit.[30,31]

Calcitonin has been used in the treatment of phantom limb pain.[34] It can be given intranasally or as an intramuscular or subcutaneous injection. The intranasal preparation is associated with fewer side effects but may cause rhinitis or epistaxis. Avoid use in patients allergic to salmon.

SPECIAL CONDITIONS

The IASP review indicates that TCAs should be considered for patients with central poststroke pain (CPSP), α2δ ligands for patients with spinal cord injury, and cannabinoids for multiple sclerosis-related NP.[31] Concerns for cannabinoid use include psychotic reactions, limited evidence, and limited availability.

A recent review[59] of the treatment of CPSP reported that there is very little evidence upon which to base treatment recommendations. The placebo controlled trials typically use small numbers over relatively short periods of time. Given these limitations, amitriptyline and lamotrigine were the only oral medications shown to be effective in placebo controlled trials[59]; gabapentin showed benefit in anecdotal reports. No other TCA, except clomipramine, has been studied in CPSP but is presumed that other TCAs are worthwhile trying based on the efficacy of amitriptyline.[59] It is thought that if antidepressants are started within a year of the stroke, pain benefit may be greater than if started later.[34]

SEROTONIN SYNDROME

Serotonin syndrome is a constellation of symptoms that include mental changes, autonomic instability, neuromuscular events, and GI effects. These symptoms range from mild to severe resulting from an increase in central serotonin as a result of medications/medication combinations. It is thought that overstimulation of the 5HT1A receptor is associated with hyperactivity, anxiety, and hyperreflexia and overstimulation of the 5HT2A receptor is associated with hyperthermia, incoordination, and neuromuscular excitement.[60] Stimulation of the 5HT3 receptors is likely responsible for nausea, vomiting, and abdominal pain.[60] Other symptoms include (but are not limited to) hallucinations, confusion, lethargy, myoclonus, muscle rigidity, and sweating. Early symptoms are generally mild and are often overlooked as they tend to mimic a viral infection. If allowed to progress, symptoms become more widespread and severe; fatalities have been reported. Treatment consists of stopping the offending agents and providing supportive care.[60] Most cases resolve within 24 hours if recognized early.[60] Serotonergic medications include but are not limited to lithium, trazodone, SSRIs, SNRIs, St Johns Wort, TCAs, and triptans. A more complete list of serotonin agents may be found elsewhere.

CONCLUSIONS

The pharmacotherapeutic management of NP is facilitated by patient-specific, patient-centered, patient-focused, personalized pharmacotherapeutic care. Therapies in the older patient are initiated with the lowest dose and then followed with planned titrations either incrementally or decrementally as a function of either response, lack of response, or side effects.

Polymodal, multimodal, pharmacologic, approaches are frequently employed utilizing various receptor specific mechanism and in a stratified manner. Many patients are able to increase functionality and activities of daily living by utilizing polymodal therapies. Further research is needed to clarify the value of polymodal therapy used in combination with antiepileptic drug (as topiramate, gabapentin), blockers (as lidocaine topical 5% patch) and opioids in a stratified care management plan.

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