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REVIEW

Options for treating postherpetic neuralgia in the medically complicated patient

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Patricia Bruckenthal[1]
Robert L Barkin[2,3]

[1]Department of Graduate Studies in Advanced Practice Nursing, Stony Brook University School of Nursing, Stony Brook, NY, USA; [2]Department of Anesthesiology, Family Medicine, and Pharmacology, Rush University Medical College, Chicago, IL, USA; [3]Department of Anesthesiology, Northshore University Health System Pain Centers, Skokie and Evanston Hospitals, Skokie and Evanston, IL, USA

Abstract: Patients with postherpetic neuralgia (PHN) are often of advanced age or immunocompromised and likely to have ≥1 comorbid medical condition for which they receive ≥1 medication (polypharmacy). Comorbidities affecting renal or hepatic function can alter pharmacokinetics, thereby impacting the efficacy or tolerability of PHN analgesic therapies. Cardiovascular, cerebrovascular, or psychiatric comorbidities may increase patient vulnerability to potential adverse events associated with some PHN analgesic therapies. Because PHN is a localized condition, localized therapy with a topical analgesic (lidocaine patch 5% and capsaicin 8% patch or cream) may provide adequate efficacy while mitigating the risk of systemic adverse events compared with oral analgesics (eg, tricyclic antidepressants, anticonvulsants, opioids). However, combined therapy with a topical and an oral analgesic or with >1 oral analgesic may be needed for optimal pain management in some patients. This review summarizes how comorbidities and concomitant medications should be taken into account when selecting among available pharmacotherapies for PHN and provides recommendations for the selection of therapies that will provide analgesia while minimizing the risk of adverse events.

Keywords: calcium channel α2-δ ligand, comorbidities, lidocaine patch, polypharmacy, postherpetic neuralgia, TCA

Introduction

The incidence of postherpetic neuralgia (PHN) increases with age.[1,2] The estimated incidence of acute herpes zoster (AHZ) infection from a population-based survey (Olmstead, MN, USA) increased dramatically with age, from 2.3 cases per 1,000 person–years (age 40–49 years) to 4.7 cases (age 50–59 years), 7.1 cases (age 60–69 years), 10.0 cases (age 70–79 years), and 12.0 cases (age ≥80 years) per 1,000 person–years.[2] Of these individuals, the proportion who develop PHN (defined in the Olmstead survey as AHZ–associated pain lasting ≥90 days) also increased with age, from 5% in individuals <60 years of age to 10% in those aged 60 to 69 years, 17% in those aged 70 to 79 years, and 20% in individuals aged ≥80 years.[2]

As with PHN, other medical conditions become more prevalent with age. For example, older individuals have an increased risk of cardiovascular disease,[3] and renal[4,5] and hepatic dysfunction[6] naturally increases with age. Older patients frequently take multiple medications for comorbid conditions,[7,8] making drug interactions common in this population.[9] PHN does, however, occur in younger individuals, particularly those who are immunocompromised because of medical conditions such as human immunodeficiency virus or multiple sclerosis.[2]

Correspondence: Patricia Bruckenthal
Stony Brook University School of Nursing, Department of Graduate Studies in Advanced Practice Nursing, Stony Brook University, HSC L2, Room 209, Stony Brook, NY 11794-8240, USA
Tel +1 631 444 3268
Fax +1 631 444 3136
Email patricia.bruckenthal@stonybrook.edu

Thus, many who have PHN are individuals with comorbid conditions who are taking multiple medications. Nonetheless, current treatment guidelines for PHN are mainly based on evidence from randomized controlled clinical trials,[10] which may exclude patients with certain comorbidities, patients taking certain medications, or patients who are outside a prespecified age range.[11] This review will summarize how comorbidities and concomitant medications should be taken into consideration when selecting appropriate therapeutic agents to alleviate PHN pain.

Search methodology

Articles cited in this review were identified via a search of PubMed for literature published in English from February 15, 2003, through February 14, 2013, including clinical trials, guidelines, meta-analyses, systematic reviews, and case reports but excluding narrative reviews, letters, and expert opinion articles. With these limitations, 150 articles were identified using the search string "postherpetic neuralgia AND (tricyclic antidepressant* OR amitriptyline OR nortriptyline OR desipramine OR anticonvulsant OR gabapentin OR pregabalin OR carbamazepine OR oxcarbazepine OR lamotrigine OR serotonin norepinephrine reuptake inhibitor OR duloxetine OR venlafaxine OR selective serotonin reuptake inhibitor OR lidocaine OR capsaicin OR opioid* OR tapentadol OR tramadol)". Articles were selected that discussed comorbidities and adverse events; in addition, searches were performed for each medication term combined with the following general search terms: active metabolites; addiction; adverse effects, safety or toxicity; cardiovascular disease; cerebrovascular disease, dementia, or brain injury; drug interactions; formulations; hepatic impairment; pharmacokinetics; pharmacology; psychiatric illness; receptor binding; receptor; renal impairment; respiratory disease. The reference lists of relevant papers were examined for additional articles of interest, and the authors included further articles with which they were familiar and considered helpful to introduce and discuss the topic.

Drugs recommended for postherpetic neuralgia

First-line therapies

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are recommended as first-line therapies for neuropathic pain in US,[12] European,[13] Canadian guidelines,[14] and international expert consensus recommendations.[15] Their efficacy has been established in randomized controlled trials in patients with PHN. In meta-analyses, numbers needed to treat (NNT) with a TCA (amitriptyline, nortriptyline, desipramine) for a 50% reduction in PHN pain ranged from 2.5 to 2.7.[16–18]

However, adverse events associated with TCAs include anticholinergic effects (eg, xerostomia, urinary retention, constipation) and orthostatic hypotension.[19] Cardiotoxicity with TCAs has also been reported, including an increased risk of myocardial infarction.[20–22] As discussed in a later section, anticholinergic and cardiovascular effects are important in several patient populations. Guideline recommendations are summarized in Table 1.

Calcium channel α2-δ ligands

Like the TCAs, the calcium channel α2-δ ligands gabapentin and pregabalin are consistently recommended as first-line therapy for neuropathic pain across treatment guidelines.[12–15] In a meta-analysis, the NNT for a 50% reduction in pain were 4.39 with gabapentin and 4.93 with pregabalin.[17] However, in Cochrane reviews, the NNT was higher for gabapentin (7.5) and lower for pregabalin (3.9).[23,24]

In pooled analyses, the most common adverse events with gabapentin have been dizziness (up to 10%–21%),

Table 1 Drugs recommended as therapy for postherpetic neuralgia

	American academy of neurology 2004[12]	Canadian pain society 2007[14]	International association for the study of pain 2010[10]	European federation of neurological societies 2010[13]
Tricyclic antidepressants	First-line	First-line	First-line	First-line
Anticonvulsants				
Gabapentin	First-line	First-line	First-line	First-line
Pregabalin	First-line	First-line	First-line	First-line
Lidocaine patch 5%	First-line	Second-line	First-line	First-line
Tramadol	First-line[a]	Third-line	Second-line	Not recommended
Opioids	First-line	Third-line	Second-line	Second-line
Capsaicin 8% patch	Second line	No recommendation	Third-line	Second-line
Capsaicin cream	Second-line	No recommendation	No recommendation	Second-line

Note: [a]Grouped with opioids.

somnolence (7%–16%), peripheral edema (1%–8%), gait disturbance (9.0%), diarrhea (5.0%), nausea (3.7%), and headache (3.1%).[24,25] In a meta-analysis of eleven clinical trials,[26] adverse events in patients with PHN treated with pregabalin included dizziness (7%–49%), somnolence (7%–29%), peripheral edema (5%–17%), xerostomia (0%–14%), weight gain (1%–13%), infection (1%–16%), and asthenia (3%–10%).[26] According to a Cochrane review, dizziness was reported in 35% of patients with PHN receiving pregabalin 600 mg;[23] this is generally consistent with the aforementioned meta-analysis, which found 30% to 49% of patients reporting dizziness while receiving pregabalin 600 mg.[26] In general, the occurrences of dizziness, somnolence, and peripheral edema increased with age, whereas the occurrences of xerostomia and weight gain decreased with age.[26]

Lidocaine patch 5%

Lidocaine patch 5% is recommended as a first-line therapy for PHN in US,[12] European,[13] and international[15] neuropathic pain guidelines and expert consensus recommendations, and topical lidocaine formulations are considered a second-line therapy in the Canadian guidelines.[14] The lidocaine patch 5% has demonstrated efficacy and generally good tolerability in patients with PHN who participated in an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled trial[27] or in a long-term, open-label study.[27,28] In head-to-head trials, lidocaine patch 5% was more effective than pregabalin.[29,30]

In the first of two head-to-head trials,[29] percentage reductions in Numerical Rating Scale (NRS-3) scores during 4 weeks of treatment were 36.3% with lidocaine patch 5% versus (vs) 29.8% with pregabalin. The proportion of patients who experienced a ≥30% improvement in NRS-3 score was higher with lidocaine patch 5% than with pregabalin (57.8% vs 48.8%), as was the proportion who experienced a ≥50% improvement (35.6% vs 20.9%).

In the second comparative trial,[30] reductions in Short-Form McGill Pain Questionnaire scores during 4 weeks of treatment improved by 40.0% in the lidocaine patch 5% group and 30.1% in the pregabalin group. The proportion of patients who experienced sufficient analgesia, defined as an absolute NRS-3 score ≤4 (ten-point scale), was higher in the lidocaine group (25 of 50; 50%) than in the pregabalin group (14 of 48; 29.2%).

Lidocaine patch 5% was better tolerated than pregabalin in the head-to-head trials.[29,30] Adverse events with lidocaine patch 5% consisted primarily of application-site reactions, whereas adverse events with pregabalin included central nervous system events: dizziness, fatigue, somnolence, vertigo, and headache.[29,30]

Second-line or third-line therapy

Opioids

Opioids (oxycodone,[31] morphine, and methadone[32]) have shown efficacy in patients with PHN. The NNT from these trials was 2.67, which is virtually identical to the NNT reported for TCAs in the same meta-analysis.[17] Morphine and methadone have shown a nonsignificant trend toward greater pain relief compared with the TCAs nortriptyline and desipramine.[32] Adverse events included those usually reported with opioid analgesics, including nausea, constipation, dizziness, xerostomia, anorexia, and sedation/somnolence.[31,32]

Despite the efficacy of opioids, opinion varies about their place in the treatment of PHN. US guidelines issued in 2004 list opioids as a first-line therapy for PHN.[12] Subsequent guidelines issued by the International Association for the Study of Pain (2007)[15] and European Federation of Neurological Societies (EFNS; 2010)[13] recommend them as second-line therapy, whereas Canadian guidelines (2007)[14] list them as a third-line option. The secondary place of opioids clearly reflects concerns about adverse events and abuse potential. Surveys of physicians have repeatedly shown that prescribers are particularly concerned about the risk of abuse.[33–35]

Tramadol

Tramadol combines opioid agonism with serotonin–norepinephrine reuptake inhibition. Like pure opioids, tramadol has shown efficacy in patients with PHN[36] but is nonetheless listed as second-[15] or third-line[14] therapy in international neuropathic pain guidelines.[15] EFNS guidelines state that tramadol is ineffective for PHN and do not recommend it for this indication.[13] According to meta-analysis, tramadol has shown less efficacy than strong opioids (NNT, 4.76).[17]

Topical capsaicin

Capsaicin (0.075%) cream or high-dose (8%) capsaicin patch works by activating local nerve fibers at the application site, which then become desensitized for a period of time.[40] A Cochrane review calculated an NNT for capsaicin cream of 6.6 (six studies) for any improvement of pain; the NNT for a ≥30% improvement in pain with capsaicin 8% patch was 12 (two studies).[41] However, in clinical trials, capsaicin 8% patch has been associated with mean improvements in numeric pain rating scale scores of ~30% for up to 3 months with a single application.[42,43]

In a meta-analysis of six double-blind, placebo-controlled trials, 54% of patients receiving capsaicin cream had application-site pain and 13% of patients withdrew from treatment owing to adverse events.[44] The capsaicin 8% patch must be administered under medical supervision in the clinician's office with local anesthetic during application; postprocedure analgesia is necessary in many patients.[45]

Additional therapies not recommended

Several medication classes have proven ineffective in patients with PHN. These include topical benzydamine, dextromethorphan, fluphenazine, memantine, lorazepam, mexiletine, and cyclooxygenase-2 inhibitors.[13] Several medications that have shown evidence of efficacy for other neuropathic pain conditions have not been studied in patients with PHN, including the serotonin–norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine and the dual opioid/SNRI tapentadol.

Interaction of analgesics with concomitant medications

Polypharmacy

Polypharmacy[46] is common in several patient populations, including older patients, patients with cancer, and patients with at least one comorbidity using multiple medications.[8,46–48] The more medications a patient receives, the greater the risk for drug–drug interactions (DDIs). DDIs in patients receiving multiple medications may affect the pharmacokinetics (ie, absorption, distribution, metabolism, excretion) and pharmacodynamics of drugs prescribed for PHN. Polypharmacy is likely to be an issue for a substantial proportion of patients with PHN, who are likely to be older and therefore have multiple conditions for which they receive medications. In a survey of 3,005 US adults aged 57 to 85 years,[7] 29% of all subjects used five or more medications daily, with the percentage increasing with age to 36% of women and 37% of men in subjects aged 75 to 85 years.

Pharmacokinetic interactions

Systemic therapies

Pharmacokinetic DDIs are dependent largely on the metabolic pathway of the medications taken, although DDIs may also be predisposed by genetic factors with certain medications. Some drugs recommended for the treatment of PHN undergo Phase 1 metabolism by the hepatic cytochrome P450 enzymes (most commonly CYP3 A4 and CYP2D6), which gives these agents a greater DDI potential than drugs undergoing Phase 2 metabolism via glucuronidation. Drugs may also inhibit or induce cytochrome P450 enzymes, thereby altering the pharmacokinetics of concurrent medications that are metabolized by these enzymes.[49,50]

Cytochrome P4503A4-mediated interactions are largely predictable and can usually be addressed by adjusting the drug dose, whereas CYP2D6-mediated interactions depend on concurrent medications and genetic factors. Up to 10% of white people have a genetic predisposition to poor CYP2D6 metabolism,[51,52] and up to 7% have genetic factors that make them rapid CYP2D6 metabolizers.[53,54] Varying degrees of rapid or reduced CYP2D6-mediated metabolism have also been described in African[55–57] and Asian[58] populations.

As shown in Table 2, three TCAs (amitriptyline, nortriptyline, and desipramine) recommended for patients with PHN are metabolized by CYP2D6,[49] conferring on them pharmacokinetic variability that is genetically based or dependent on concurrent administration of drugs that are substrates of CYP2D6. Amitriptyline, desipramine, and nortriptyline are CYP3A4 inhibitors,[50] giving them the potential to alter the pharmacokinetics of calcium channel blockers, statins, warfarin, phosphodiesterase inhibitors, selective-serotonin reuptake inhibitors (SSRIs), sleep aids (zolpidem, zopiclone), hormone therapies, and antiretrovirals.

Gabapentin and pregabalin are excreted as unchanged drug in urine and are not appreciably metabolized in humans[59,60] and therefore have little potential for pharmacokinetic interactions. Opioids that do not undergo significant CYP metabolism (eg, morphine,[61] hydromorphone,[62] oxymorphone[63]) have few DDI risks.[64] Conversely, fentanyl, hydrocodone, methadone, oxycodone, and tramadol are each metabolized by at least one CYP enzyme, conferring DDI risk on these agents.[64] In particular, methadone undergoes complex metabolism involving six CYP enzymes, necessitating special caution in patients who are taking multiple medications.[65]

Topical therapies

Lidocaine patch 5% is not associated with significant systemic lidocaine exposure[66–68] and therefore has little potential to cause DDIs. However, caution is needed in patients concomitantly receiving lidocaine and antiarrhythmic medications, especially in patients with severe hepatic disease, who have an inability to metabolize lidocaine.[69] There are no known clinically meaningful interactions with topical capsaicin preparations,[45] which do not accumulate in the system even when applied as a high-dose capsaicin 8% patch.[70]

Pharmacodynamic interactions

Potential for antagonistic, synergistic, or additive pharmacodynamic DDIs exist. TCAs have additive effects and should

Table 2 Potential drug–drug interactions of drugs commonly prescribed for postherpetic neuralgia

Drug	Metabolic pathway[a]	Pharmacokinetic interactions	Pharmacodynamic interactions
Generally first-line therapies			
Tricyclic antidepressants			
Amitriptyline	CYP2D6[49,50]	CYP2D6 substrates, CYP3A4 inhibitor[49,50]	Anticholinergic drugs (additive) Sympathomimetic drugs (additive) CNS depressants (additive) MAOIs, guanethidine, thyroid medications, disulfiram (additive)[71]
Nortriptyline	CYP2D6[49,50]	CYP2D6 substrates, CYP3A4 inhibitor[49,50]	Anticholinergic drugs (additive) Sympathomimetic drugs (additive) Chlorpropamide (hypoglycemia)[72]
Desipramine	CYP2D6[49,50]	CYP2D6 substrates, CYP3A4 inhibitor[49,50]	Anticholinergic drugs (additive) Sympathomimetic drugs (additive) CNS depressants (additive)[73]
Clomipramine	CYP2D6[49,50]	CYP2D6 substrates[49]	Anticholinergic drugs (additive) Sympathomimetic drugs (additive) CNS depressants (additive) Highly protein-bound drugs (eg, warfarin, digoxin)[80]
Calcium channel α2-δ ligands			
Gabapentin[60]	None	Hydrocodone (reverse) Morphine (↑ gabapentin concentrations)	Minimal interaction potential
Pregabalin[59]	None	Minimal interaction potential	Oxycodone (additive) Lorazepam (additive) Thiazolidinedione (additive)
Lidocaine patch 5%[69]	None	None	Antiarrhythmics (additive)[b]
Generally second-line therapies			
Opioids[64]			
Codeine	CYP2D6/ glucuronidation	CYP2D6 substrates, inhibitors, and inducers	Anticoagulants (additive) CNS depressants (additive)
Fentanyl	CYP3A4	CYP3A4 substrates, inhibitors, and inducers	CNS depressants (additive)
Hydrocodone	CYP2D6/ glucuronidation	CYP2D6 substrates, inhibitors, and inducers	CNS depressants (additive)
Hydromorphone	Glucuronidation	Minimal interaction potential	CNS depressants (additive)
Methadone	CYP2B6 CYP2C8 CYP2C19 CYP2D6 CYP2C9 CYP3A4	CYP substrates, inhibitors, and inducers	CNS depressants (additive) Arrhythmogenic agents – Class I and II (additive) TCAs, CCBs, antipsychotics – selected (additive) Diuretics and laxatives
Morphine	Glucuronidation	Minimal interaction potential	CNS depressants (additive)
Oxycodone	CYP3A4/ CYP2D6	CYP3A4 substrates, inhibitors, and inducers/ CYP2D6 substrates, inhibitors, and inducers	CNS depressants (additive)
Oxymorphone	Glucuronidation	Minimal interaction potential	CNS depressants (additive)
Tramadol	CYP3A4, 2D6, 2B6	CYP3A4 substrates, inhibitors, and inducers CYP2D6 substrates, inhibitors, and inducers	CNS depressants (additive) SSRIs, TCAs, SNRIs, MAOIs, cyclobenzaprine, triptans (additive)
Capsaicin patch[45]	None	None	None

Notes: [a]Several opioids undergo CYP-mediated metabolism to metabolites that require glucuronidation. For example, codeine is metabolized to morphine, which then undergoes glucuronidation; [b]this warning is for all formulations of lidocaine, including injectable formulations.

Abbreviations: CCBs, calcium channel blockers; CNS, central nervous system; CYP, cytochrome P450; MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

be used cautiously with other drugs that have cholinergic or sympathomimetic effects (eg, pseudoephedrine).[71–73] Desipramine reportedly has additive effects with tranquilizers or sedative/hypnotics.[73] Caution is needed with the concomitant administration of pregabalin and a thiazolidinedione because of the combined potential for weight gain and peripheral edema.[59]

Opioids have additive effects with other drugs that depress the central nervous system. Tramadol, like pure opioids, also has additive effects with these agents and additive

effects with other serotonergic drugs.[64] Coadministration of tramadol with other serotonergic drugs (eg, SSRIs) or opioids (ie, hydrocodone, morphine) has been associated with an increased risk of serotonin syndrome.[74–76] Based on these potential effects, the maximum recommended dose of tramadol ER should not exceed 300 mg/day.[77]

As with pharmacokinetic interactions, application of the topical agents lidocaine patch 5% and capsaicin 8% patch result in low systemic drug exposure and are not likely to exert additive effects with other agents.[66–68]

Common comorbidities

Just as PHN becomes more common with age, comorbid diseases that complicate its treatment also become more prevalent with age. Various conditions (eg, renal and hepatic impairment; cardiovascular, cerebrovascular, and respiratory disease; brain disorders; and psychiatric conditions) have the potential to alter the tolerability or efficacy of drugs prescribed for PHN either directly or as a result of polypharmacy.

Renal disease

Recommendations for the use of PHN therapies in patients with altered renal function are summarized in Table 3. Renal function in normal individuals declines by an estimated 0.75 mL/minute annually after the fourth decade of life.[4] At this rate, an 80-year-old individual with normal age-related decline in renal function may have two-thirds the renal function expected in individuals in their 20s.[4,5] Renal impairment is characterized by a creatinine clearance rate ≤80 mL/minute/m^2.[78] The prevalence of renal disease increases with age, climbing from <1% in individuals aged 18 to 44 years to nearly 5% in individuals aged ≥75 years.[79] Thus, the older patients who make up the majority of patients with PHN are likely to require dosage adjustments, either because of normal aging or renal disease.

Renal impairment may influence the selection of a first-line therapy or prompt a switch from a first-line therapy to a second- or third-line therapy (Table 3). For TCAs, dosage adjustments are recommended in older patients treated with desipramine because of anticipated age-related reduction in renal clearance of the drug,[73] and caution is recommended when using clomipramine in patients with renal impairment.[80] Because gabapentin and pregabalin are mainly eliminated unchanged by the kidney, they should be administered with caution in patients with creatinine clearance ≤60 mL/minute/m^2 following the dose adjustment table provided in the prescribing information.[59,60,67]

Most opioids are eliminated in urine, making dosage adjustments necessary.[62,63,81,82] Fentanyl appears to be relatively unaffected by renal disease, making it a potential choice in this population.[83] However, fentanyl patch is only indicated for opioid-tolerant patients because of the risk of respiratory depression.[84] Methadone is typically not

Table 3 Risks associated with drugs for postherpetic neuralgia: patients with renal or hepatic impairment or failure

Relative risk	Renal impairment/failure		Hepatic impairment/failure	
	First-line therapies	Second-line therapies	First-line therapies	Second-line therapies
Low risk	Amitriptyline[71] Nortriptyline[72] Lidocaine patch 5%[69]	Fentanyl[a,64] Capsaicin patch/cream[45]	Desipramine[73] Nortriptyline[72] Gabapentin[60] Pregabalin[59]	Fentanyl[a,64] Capsaicin patch/cream[45]
Use with caution	Clomipramine[80] Desipramine[73] Gabapentin[b,60] Pregabalin[b,59]	Tramadol[64] Methadone[64]	Amitriptyline[71] Clomipramine[80] Lidocaine patch 5%[c,69]	Hydromorphone[64] Morphine[64] Oxycodone[64] Methadone[64]
Avoid	NA	Codeine[64] Hydrocodone[64] Morphine[64] Tapentadol[d,37]	NA	Codeine[64] Oxymorphone[64] Tramadol[64] Tapentadol[d,37]
Limited information	NA	Hydromorphone[64] Oxycodone[64] Oxymorphone[64]	NA	Hydrocodone[64]

Notes: [a]Not recommended in opioid-naive patients; [b]dose should be adjusted based on creatinine clearance in older patients suspected of having renal impairment; [c]patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine because of their inability to metabolize lidocaine normally; [d]not recommended in patients with severe renal or hepatic impairment; may use with caution in patients with moderate hepatic impairment, and no dose adjustment is needed in patients with mild hepatic impairment.

Abbreviation: NA, not applicable.

recommended as a first-line therapy, particularly in older patients using polypharmacy, because it has a narrow therapeutic index and exhibits highly variable pharmacokinetics; methadone should also be used with caution in patients with renal impairment.[85]

Morphine, hydromorphone, and tramadol present difficulties in patients with impaired renal function in that the metabolites of morphine (morphine-3-glucuronide, morphine-6-glucuronide)[86,87] and hydromorphone (hydromorphone-6-glucuronide, hydromorphone-3-glucuronide)[88] accumulate in patients with renal dysfunction. Accumulation of either the morphine or hydromorphone metabolites has been associated with neuroexcitatory effects, including seizures, allodynia, and myoclonus.[64,89] Accumulation of morphine metabolites has also led to morphine intoxication and chronic nausea in patients with varying degrees of renal impairment.[37,64,83,90–94] Finally, tramadol is available in limited dosage strengths,[77] making dosage adjustments in patients with renal dysfunction difficult to achieve.

Hepatic dysfunction

Recommendations for the use of PHN therapies in patients with hepatic impairment are summarized in Table 3. As with kidney failure, normal aging is associated with reduced liver volume and blood flow.[6] The prevalence of liver disease reaches a peak of 2.3% between the ages of 45 and 64 years before declining to 1.5% between the ages of 65 and 74 years and 1.0% in individuals ≥75 years.[79] Hepatic impairment may result from alcoholism, chronic hepatitis B or C, hemochromatosis, biliary tract obstruction, or obesity.[95] Hepatic dysfunction might be expected to reduce first-pass drug metabolism, thereby having a greater effect on CYP450-metabolized medications than on drugs metabolized via glucuronidation. However, as discussed below, the effects of liver dysfunction on the metabolism of drugs administered to patients with PHN cannot be predicted on the basis of metabolic pathway.

Among drugs prescribed for PHN, hepatic function appears to be mainly of significant importance in its effects on opioids (Table 3). The three opioids metabolized via glucuronidation are each affected by the presence of hepatic impairment. Morphine clearance is reduced by ≥25% in patients with liver failure, making dosage adjustments necessary.[96] Hydromorphone maximal concentration and exposure may be increased up to fourfold in patients with moderate hepatic impairment,[97] and oxymorphone is contraindicated in patients with moderate to severe hepatic impairment because oxymorphone concentrations may be increased up to 12-fold.[63] Exposure to the M1 metabolites of tramadol increase by approximately 50% in patients with mild, or moderate hepatic impairment. As in renal failure, the limited number of tramadol doses available, make it difficult to make dose adjustments in patients with hepatic impairment.[37,64] Conversely, the pharmacokinetics of fentanyl are largely unaffected by liver dysfunction, even though this drug undergoes CYP3A4-mediated metabolism.[98]

There are no particular precautions for TCAs in patients with hepatic impairment, although the product label for amitriptyline recommends low initial doses in older patients partly because of the aforementioned age-related decrease in hepatic function.[71] The label for clomipramine recommends caution when treating patients with known liver disease and recommends monitoring liver enzymes in these patients.[80] Gabapentin and pregabalin are excreted as unchanged drug and are therefore not substantially altered by hepatic function.[59,60] Lidocaine patch 5%, although generally safe in the majority of patients, does have a precaution in patients with severe hepatic disease because of accumulation of lidocaine due to inability of these patients to metabolize lidocaine.[68]

Cardiovascular and respiratory disease

The relative safety of PHN therapies in patients with cardiovascular or respiratory disease are summarized in Table 4. Cardiovascular disease becomes more common with

Table 4 Drugs for postherpetic neuralgia: relative risk in patients with cardiovascular or respiratory disease, cerebrovascular disease, or brain disorders

Relative risk	First-line therapies	Second-line therapies
Cardiovascular or respiratory disease		
Low risk	Gabapentin[60]	Tramadol[64,109]
	Pregabalin[59]	
	Lidocaine patch 5%[69]	
Use with caution	TCAs[a,71–73,80]	Morphine[64]
		Oxycodone[64]
		Oxymorphone[64]
		Fentanyl[b,64]
		Capsaicin patch[42,45,99]
Avoid	NA	Methadone[64]
		Codeine[64]
Cerebrovascular disease/brain disorders		
Relative risk	First-line therapies	Second-line therapies
Low risk	Lidocaine patch 5%[69]	
Use with caution	TCAs[32,111]	Capsaicin patch[45]
	Gabapentin[24]	Most opioids[113–116]
	Pregabalin[23]	
Avoid	NA	Morphine[114–116]
		Hydromorphone[113,117]

Notes: [a]Avoid in patients with heart failure; [b]not recommended in opioid-naive patients.
Abbreviations: NA, not applicable; TCA, tricyclic antidepressant.

increased age; the incidence of a first cardiovascular event increases from three cases per 1,000 in men between the ages of 35 and 44 years to 74 cases per 1,000 in men aged 85 to 94 years.[3] Similar incidence rates occur a decade later in women, although the gap narrows with age.[3] The prevalence of emphysema and chronic bronchitis also increase with age, whereas the prevalence of allergic conditions or sinusitis decrease or remain stable.[79]

Of first-line therapies, only TCAs have been associated with an increased risk of cardiovascular events (Table 4). Specifically, separate analyses found that treatment with TCAs was associated with a 2.2-fold increase in the risk of myocardial infarction and a 1.67-fold (200 mg/day) or 2.53-fold (≥300 mg/day) increase in the risk of sudden cardiac death compared with untreated controls.[20–22] These agents should be used cautiously in patients with heart disease or significant cardiovascular risk factors and are contraindicated during the acute recovery phase following a myocardial infarction.[71–73,80] Although not associated with cardiovascular events, gabapentin and pregabalin may cause weight gain[59,60,66,68] and peripheral edema, which may make it more difficult to clinically assess weight gain and edema in patients with congestive heart failure or peripheral vascular disease.[42,45,67,99]

Research suggests that older (>70 years) patients are more susceptible to respiratory effects of opioids.[100] All opioids have the potential for cardiovascular and respiratory depressive effects and should be used with caution in patients with cardiovascular or respiratory disease.[64] In addition, several opioids require special caution in patients with heightened cardiovascular risk. Methadone has caused time- and dose-related QTc interval prolongation and arrhythmias (some fatal).[101,102] Morphine has produced profound respiratory depression in patients with heart failure,[103] chronic obstructive pulmonary disease,[104] and sleep apnea.[105,106] In a head-to-head trial, oxycodone produced significant respiratory depression, whereas tramadol did not have any effect on respiratory parameters.[107,108] Tramadol may be a comparatively safe option in patients with PHN and cardiovascular risk factors for whom first-line therapies or other opioids are not considered appropriate.[109]

Application of lidocaine patch 5% at recommended doses (up to 4 patches daily) produces systemic lidocaine concentrations <200 mg/mL, which is much lower than the concentrations required to cause cardiovascular effects (1,500 mg/mL) or cardiotoxicity (5,000 mg/mL). Capsaicin 8% patch has been associated with transient, and potentially serious, increases in blood pressure. These increases seem to result from treatment-related pain because blood pressure rises with patch application but declines with topical anesthetic application. Caution with capsaicin is therefore advised in patients with poorly controlled hypertension or a history of cardiovascular or cerebrovascular events.

Cerebrovascular disease and brain disorders

Several drugs prescribed for patients with PHN increase the risk of cognitive impairment, seizures, and falls in patients with dementia, traumatic brain injury, a history of stroke, or other brain disorders or injuries (Table 4). In addition to dementia risk, the prevalence of stroke[3] and of risk factors for stroke[3,110] (eg, diabetes, hypertension) increase with age,[79] making them conditions of concern in the population that is most likely to develop PHN.

TCAs are associated with central (eg, memory and cognitive impairment) anticholinergic effects. Patients with dementia, seizure disorders, stroke, or other brain injuries have been excluded from clinical trials, but anticholinergic effects have nonetheless been reported in these carefully selected study populations.[32,111] TCAs lower the seizure threshold in vulnerable populations, including those with epilepsy and a prior history of stroke. Neither electrocardiogram findings nor plasma TCA levels are of predictive value for determining the risk of stroke, making it advisable to avoid TCAs in these patients.[112] Gabapentin or pregabalin may cause dizziness and somnolence.[23,24] Withdrawal seizures may occur if these agents are abruptly discontinued.[59,60]

Cognitive impairment, delirium, and hallucinations have been reported to occur with the administration of opioids.[113–116] These effects may be more pronounced with morphine[114–116] or hydromorphone,[113,117] which have metabolites that may be neuroexcitatory when they accumulate. The presence of cerebrovascular disease or a brain disorder should not alter the efficacy or tolerability of the topical therapies lidocaine[45] patch 5% and capsaicin cream or 8% patch.

Limited routes of administration

For patients who are unable to swallow tablets or capsules, nortriptyline,[118] gabapentin,[119] and pregabalin[120] are available in oral solutions. Topical lidocaine, topical capsaicin, and the Fentanyl transdermal patch are options that eliminate the need for swallowing altogether.[84]

Psychiatric illness and addiction

The product labels for TCAs warn of the potential for increased risk of suicide and suicidal ideation.[71–73,80]

However, a meta-analysis of trials evaluating antidepressants, including TCAs, found that any contribution of antidepressants to suicidal behavior occurs exclusively in patients aged <25 years,[121] an age group that is largely unaffected by PHN. The US product labels for antiepileptic drugs, including gabapentin and pregabalin,[59,60] also include warnings that these agents may cause suicidal behavior and ideation, and data from a cohort study has indicated an increased risk with several antiepileptic agents, including gabapentin.[122] However, a pharmacoepidemiologic study of gabapentin alone found that it had no effect on suicide risk in nonpsychiatric patients and a reduced risk in patients with bipolar disorder, major depression, and other psychiatric disorders.[123] There are no published clinical trials or case reports of suicides or suicidal ideation patients treated with pregabalin.

Psychiatric disorders, such as depression and anxiety, have been shown to be associated with increased opioid use.[124] It is important to remember that older individuals who are at greatest risk for PHN may express depression or anxiety as somatic complaints,[125] making it essential to carefully assess the psychological status of the older patients to ensure that somatic complaints and psychiatric issues are addressed.

It is important to note that the risk of abuse and the proportion of opioid-treated patients who abuse these drugs decreases with age.[126] Hence, initiating first-time opioid therapy in an older patient with PHN might be less of a risk than in younger patients. However, past or current abuse of opioids or other substances is a significant risk factor for future abuse,[127] making it essential for prescribers to evaluate all opioid-treated (and other controlled substances) patients before initiating therapy[128] and to conduct periodic compliance monitoring using comprehensive urine drug testing.[129]

Conclusion

Postherpetic neuralgia occurs most frequently in older individuals, many of whom have multiple medical comorbidities and receive multiple medications, and in individuals who are immunocompromised and therefore likely to be in poor health and receiving multiple medications. Available therapies include several systemic therapies, including TCAs, calcium channel α2-δ ligands (gabapentin and pregabalin), opioids, and tramadol, as well as two topical therapies, lidocaine patch 5% and capsaicin cream or 8% patch. Generally, systemic therapies are more likely than topical therapies to present problems of tolerability in medically complicated patients because of comorbid disease states and pharmacokinetic drug interactions. Adequate consideration of comorbid medical conditions and careful drug selection in the medically complicated patient with PHN is therefore essential to ensure adequate disease management with a minimum of risk.

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Disclosure

Dr Barkin has served on speakers' bureaus for Endo Pharmaceuticals, and Eli Lilly, and has presented research at scientific congresses with reimbursement of associated expenses from Endo Pharmaceuticals. Dr Bruckenthal served on an advisory board for Endo Pharmaceuticals. Dr Bruckenthal and Dr Barkin have authored review articles with support of medical writing assistance from Endo Pharmaceuticals Inc (Malvern, PA, USA), but have not received honoraria for these projects. The authors report no other conflicts of interest.

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