Section 1 Neurological Disorders

Chapter 1

Postherpetic neuralgia*

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Case study

A 78-year-old male with a history of postherpetic neuralgia (PHN) as well as hypertension presents to your office with complaints of moderate to severe pain (intensity 7/10) along the right T8 dermatome. He experienced acute herpes zoster (shingles) in this region 3 years ago and was treated at that time with acyclovir and analgesics. The pain never dissipated and for the past 3 years he has been treated with a variety of medications, including immediate-release gabapentin, nortriptyline, and the 5% lidocaine patch as well as unsuccessful treatment with various nerve blocks and a trial of spinal stimulation.

1. What are the basic facts regarding postherpetic neuralgia, varicella-zoster virus, and shingles?

Postherpetic neuralgia is a chronic painful complication of shingles, originating with the varicella-zoster virus (VZV), the same virus that causes chicken pox. Approximately, 98% of adults have been exposed to VZV, mostly as children. Reactivation of VZV can occur decades after initial exposure to the virus. Shingles occurs in approximately 1 million people/year in the USA alone and thus, it is the neurological disease with the highest incidence in the USA. There is a one out of three lifetime incidence in the general population of developing shingles, with increasing incidence in the elderly. Between 40% and 50% of the people who develop shingles are older than 60 years of age and between 10% and 20% develop PHN.[1,2] PHN results from damage to sensory neurons caused by reactivation of VZV. In PHN, residual nerve fibers appear to become hyperexcitable, resulting in persistent and unpredictable neural signaling, producing a pain state that is often difficult to manage. PHN is described as the pain that persists 3 months or more beyond the healing of herpes zoster blisters and approximately 15% of people who have had shingles ultimately develop PHN. In the USA, this translates to approximately 150 000 new cases annually.[3]

2. What are the basic features of postherpetic neuralgia?

Symptoms of PHN may last indefinitely. Risk factors for PHN include female gender, advanced age, presence of painful VZV prodrome, greater VZV rash severity or significant pain, elevated fever in the acute phase of the VZV episode, and sensory dysfunction in the affected dermatome. As with VZV, PHN disproportionately affects older patients.[4] In one study, the overall incidence of PHN was 18% in all adults, but increased to 33% for those $\geq$ 79 years.[5]

3. Why are there are so many challenges with regard to postherpetic neuralgia treatment options?

Numerous pharmacologic options for PHN have been extensively studied in randomized controlled studies, and several guidelines regarding the pharmacologic treatment of PHN itself exist. Treatment success must overcome a series of barriers. First, the PHN patient

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Case Studies in Pain Management, ed. Alan David Kaye and Rinoo V. Shah. Published by Cambridge University Press.

Table 1.1. Summary of treatment guidelines for PHN*

	NeuPSIG (2010)	EFNS (2010)	CPS (2007)	AAN (2004)
Alpha-2 delta ligands†	1st line	1st line	1st line	1st line
TCAs‡	1st line	1st line	1st line	1st line
Topical lidocaine	1st line	1st line	2nd line	1st line
Opioids (including tramadol)	2nd line	2nd line	3rd line	1st line
Topical capsaicin (0.025–0.075%)	2nd line	3rd line	Not described	Not described
Topical capsaicin (8%)§	–	3rd line	Not described	Not described

* Except for the AAN guidelines, all review neuropathic pain in general but make specific mention of PHN within the guidelines. All lines of therapy refer to role in PHN specifically.
† Gabapentin immediate release and pregabalin. At the time of publications of these guidelines, gastroretentive gabapentin was not available.
‡ Nortriptyline, amitriptyline, desipramine, imitriptyline. NeuPSIG distinguishes between secondary amine TCAs (nortriptyline and desipramine) and tertiary amine TCAs (amitriptyline, imitriptyline) and recommends the former due to superior tolerability.
§ Topical capsaicin (high concentration, 8%) was approved on November 16, 2009, shortly before publication of the guidelines.

population is frequently older. As with any older population, medical comorbidities and multidrug regimens may affect the choice of drug therapy. Second, not infrequently, payors may limit treatment options or require a step approach mandating failure with certain generic medications, often used in an off-label manner (including Medicare Part D providers), before paying for potentially more appropriate, as well as potentially higher cost, options. This often results not only in the use of medications that are not specifically Food and Drug Administration (FDA) approved for the treatment of PHN being used before those that are and for which there may be more data to guide treatment, but also potentially a greater likelihood of failure of treatment and its resulting impact on the patient with PHN. Third, the process required to optimize treatment for most medications used to treat PHN to ameliorate adverse effects may require long titration periods, demanding patience and education on the part of both the physician and the patient. Fourth, assuming the physician can overcome the first three barriers, the patient has, based upon the best available guidelines, literally at best, a 50/50 chance of achieving clinically meaningful pain relief (considered 30% pain intensity reduction) with little chance of predicting who will respond to a particular treatment.

4. What are the guidelines for postherpetic neuralgia management?

Over the past decade, several organizations have published guidelines either devoted exclusively to PHN or describing PHN in the context of neuropathic pain conditions in general.[6–9] A summary of their recommendations is found in Table 1.1. Each of the guidelines recognize the alpha-2 delta ligands, tricyclic antidepressants (TCAs), opioids, and tramadol as systemic options and topical lidocaine as a non-systemic approach for the treatment of localized PHN. Alpha-2 delta ligands and TCAs are typically recommended as first- or second-line status in the guidelines, and opioids and tramadol are often relegated to second- or third-line although under certain circumstances, first-line. At the time the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain (NeuPSIG) guidelines were written, the topical capsaicin (8%) patch was recognized as an emerging therapy with insufficient evidence to make a recommendation. In addition, a gastroretentive form of gabapentin as well as a form of gabapentin which is in fact a prodrug were not addressed. Table 1.2 shows the NeuPSIG guidelines. Additional evidence for the use of these agents is now available.

The NeuPSIG[7] and the European Federation of Neurological Societies (EFNS)[8] guidelines are the most recently published. Both review the treatment of neuropathic pain in general, but also include specific mention of PHN. The Canadian Pain Society (CPS), published in 2007, likewise makes specific mention of PHN within the context of overall neuropathic pain. The American Academy of Neurology (AAN), in contrast, published a specific PHN guideline in 2004; however, new published evidence has become available since 2004.

Table 1.2. Summary of NeuPSIG Guidelines for PHN*

- Begin treatment with one or more of the following:
  - Secondary amine TCA (nortriptyline, desipramine)
  - Alpha-2 delta ligand (gabapentin, pregabalin)
  - Topical lidocaine (for patients with localized PHN) alone or in combination with another therapy
  - Opioids or tramadol for patients with acute exacerbations requiring prompt relief (used alone or in combination with one other first-line therapy)
- If pain relief is partial (average pain $\geq$ 4 out of 10), add one of the other first-line therapies
- If no or inadequate pain relief (< 30% reduction at target dosage) after an adequate trial,† switch to another first-line option
- If first-line single-agent or combination therapy fails, consider second- or third-line options

* Modified from table 1 in Ref.[7].
† Some drugs such as immediate-release gabapentin and TCAs require long duration of up to 8 weeks.

Criteria for recommendations varies

The NeuPSIG guidelines rated a medication first line if it has proven effective in *multiple* randomized controlled studies (RCTs) *and* the results are consistent with the authors' clinical experience; second-line status if efficacy has been established in multiple RCTs but the authors had reservations about the use of the medication relative to first-line options; third-line if efficacy was shown in only one RCT or if the results of two or more RCTs were inconsistent, "but the authors thought that in selected circumstances the medication may be a reasonable treatment option."[8: p. S4]

In contrast, the EFNS rate medications having "established" efficacy based on class I or class II evidence, with class I defined as "an adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations" (Table 1.1).[10] In addition, class I studies must have *all* of the following: (a) randomization concealment, (b) clearly defined primary outcome(s), (c) clearly defined exclusion/inclusion criteria, (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for difference. Class II is defined as "prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one of the criteria a–e" (Table 1.1).[10]

The CPS published a consensus statement on the management of neuropathic pain in 2007.[9] To be recommended in the guidelines, medications had to show efficacy in at least one methodologically sound RCT (Level 1B or better, as defined by Ref.[11]). The guidelines state that they are based on analgesic efficacy, side effect profiles, ease of use, and cost, but describe no criteria for any of these domains except efficacy. To be recommended as first- or second-line, medications had to have high-quality evidence of efficacy and be considered straightforward to prescribe and to monitor. Medications were relegated to third-line if there was good evidence of efficacy but more specialized follow-up and monitoring were required.

The fourth guideline, and the only one to specifically address PHN, is the AAN practice parameter published in 2004. The criteria for a level A recommendation were very similar to the Brainin criteria used by the EFNS and required at least one class I study or at least two consistent, convincing class II studies. For class I and class II, the authors also calculated, if possible, absolute risk reduction, number needed to treat (NNT) for adequate pain relief, 95% confidence interval of the NNT, and number needed to harm. Recommendations were then grouped, with Group 1 medications showing medium to high efficacy, good strength of evidence, and low level of side effects, and Group 2 medications showing lower efficacy than those in Group 1 or limited strength of evidence or side effect concerns. (Three other groups with successively lower strength of evidence are also described in the AAN practice parameter.) The criteria for "medium" versus "high" level of efficacy were not defined, nor were the criteria for what constitute a "side effect concern." The AAN guidelines are somewhat dated but it is interesting to note that, of the four major drug classes currently recommended today as first-, second-, or third-line

therapy in the NeuPSIG, EFNS, or CPS guidelines, *all* of them are recommended as Group 1 medications (alpha-2 delta ligands, TCAs, opioids, and lidocaine patch) in the AAN guidelines. All drugs listed as Group 2, 3, and 4 options are now considered ineffective or unproven. More recent guidelines downgrade opioids because of the risk of abuse and the added time needed to assess risk, monitor the patient, monitor for adverse effects, and remove patients from therapy if abuse is suspected. The reader must keep in mind that these guidelines have arrived at similar BUT not identical conclusions.

5. Are there any systematic reviews and meta-analysis data on postherpetic neuralgia treatments?

In addition to the above-mentioned guidelines, four separate Cochrane reviews have been published, one each on gabapentin,[12] pregabalin,[13] topical lidocaine,[14] or topical capsaicin,[15] as well as a meta-analysis of a broad range of drugs for PHN.[16] Except for the topical lidocaine Cochrane review, which focused exclusively on PHN, the other Cochrane reviews included a range of neuropathic, and at times non-neuropathic, pain conditions. The Cochrane review on gabapentin[12] included PHN studies of immediate-release and gastroretentive gabapentin. It concluded that gabapentin was effective for chronic neuropathic pain but did not draw any conclusions specifically about efficacy in PHN. The Moore review on pregabalin[13] included 5 PHN studies and concluded that pregabalin at both 300 mg/day and 600 mg/day were effective in PHN, with greater responses seen at 600 mg/day. The Khaliq review[14] on topical lidocaine identified nine published trials but excluded seven of them because they did not meet prespecified inclusion criteria. One additional unpublished trial was identified and data were obtained from the FDA and analyzed. According to this review, these three studies demonstrated modest benefit of topical lidocaine in PHN and the authors concluded that there is insufficient evidence to recommend topical lidocaine as first-line therapy in PHN. The Derry[15] review on topical capsaicin analyzed six studies of low-concentration topical capsaicin (0.075%) cream and two studies utilizing the high-concentration topical capsaicin (8%) patch. The authors concluded that repeated daily applications of the cream and a single application of the patch (applied once every 3 months) provided "some degree of improvement" in patients with PHN.[15: p. 14] The meta-analysis conducted by Edelsberg and colleagues[16] analyzed 12 randomized controlled PHN studies involving eight different agents. This analysis demonstrated that gabapentin immediate release (2 studies), pregabalin (3 studies), the TCAs amitriptyline and nortriptyline (1 study each), morphine (1 study), capsaicin (2 studies), tramadol (1 study), and divalproex (1 study) showed statistically significantly greater reductions in pain compared with placebo. In general, the Cochrane reviews and the meta-analysis are all consistent with the recommendations of current guidelines, with the exception of the topical lidocaine Cochrane review, which did not consider sufficient evidence to exist to recommend topical lidocaine as first-line therapy.

6. Are there any gaps in the Postherpetic Neuralgia Treatment Guidelines?

High-quality clinical studies have been the foundation of evidence-based medicine and provide a solid foundation for authoritative guidelines, yet interpreting and applying the guidelines to clinical practice must be done with an awareness of the limitations and blind spots of clinical studies and a full understanding of what evidence-based medicine is and what it is not. Evidence-based medicine includes "hard" data but as defined, also allows for the integration of clinical expertise and patients' values and preferences.[17] As Sackett has stated, evidence-based medicine is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. In this definition, the practice of evidence-based medicine means integrating individual clinical expertise with a critical appraisal of the best available external clinical evidence from systematic research."[18] Regrettably, it is our view that this definition is not addressed in the guidelines described above.

Clinical trials often select patient populations to minimize intersubject heterogeneity. Specific comorbidities are often excluded, and concomitant medications that many patients would commonly take are excluded. While this approach minimizes variables that confound interpretation by doing so, it also

excludes the type of patient that is commonly seen in clinical practice. In addition, differences among formulations of the same drug in terms of efficacy, dosing, adherence, and convenience and patient preferences (which may range from dosing convenience to a specific adverse effect that a patient may find problematic) may not be addressed. Also typically not addressed are differences in tolerability in clinically relevant subpopulations; the efficacy at target doses that typically can be achieved in practice (in contrast to those achieved in clinical studies); differences in the various descriptive components of pain; acute exacerbations of pain; and onset of pain relief. Given that head-to-head studies are often lacking, direct comparisons of various pharmacologic options is difficult, and studies used to develop published guidelines, typically do not assess long-term therapy (> 3 months).

Although it would be unfair to say that PHN guidelines don't address these issues at all, if they are addressed it is often done in the context of neuropathic pain in general and lacking in direction regarding how to integrate numerous clinical variables in practice (the "real" world), particularly in complex patients who have significant medical and other comorbidities and who may be taking numerous medications. PHN guidelines, in particular, are further hampered by a lack of inclusion of more recent clinical data that have emerged since the last guidelines were published in 2010.

7. Are there any new clinical data on postherpetic neuralgia treatments?

High-concentration (8%) topical capsaicin patch

The high-concentration topical capsaicin patch is administered once every 3 months (in contrast to the low-concentration topical capsaicin creams, which are administered several times daily). Since the publication of the last guidelines, multiple publications including two multicenter, randomized, double-blind PHN studies[19,20] and an integrated analysis of four randomized, double-blind PHN studies[21] have become available. The patch was applied for 60 minutes in all studies although in one study the patch was also applied for 30 and 90 minutes.[20] Subjects in the control arms received a 0.04% capsaicin patch to maintain blinding, as a true placebo would not induce a local site reaction, which occurs with the 8% patch. The primary endpoint was change from baseline in pain intensity level assessed using a Numerical Pain Rating Scale (NPRS). Change from baseline was calculated by comparing baseline scores with the average of daily NPRS scores from weeks 2–8 and weeks 2–12. Data from Week 1 data were not included because subjects received opioid medication in week 1 to alleviate application site pain caused by the patch.

The Irving study[19] showed the high-concentration topical capsaicin patch superior to control in change from baseline in NPRS to weeks 2–8, percentage change from baseline in NPRS from weeks 2–8 and weeks 2–12, percentage of patients with a 30% response, and percentage of patients with a 50% response[19: p. 105] (Table 1.2). In the Webster study,[20] a 60-minute application showed significant improvement in percent change from baseline in average pain score (NPRS) over weeks 2–12, but no significant reduction in mean change from baseline over weeks 2–8 or weeks 2–12 or in percent change from baseline over weeks 2–8. The integrated analysis of over 1000 patients in 4 PHN studies likewise demonstrated statistically significant improvements relative to control in percentage change from baseline in NPRS to weeks 2–12, 30% response rate, and 50% response rate as well as patient global impression of change (PGIC).

Based on these data, although published guidelines did not address this treatment for the reasons noted above, it is our opinion that the high-concentration topical capsaicin patch should be considered first-line therapy for patients with localized PHN.

Gastroretentive gabapentin

Gastroretentive gabapentin is one of two currently available extended-release formulations of gabapentin. When administered with a meal, this tablet swells and resides in the stomach for up to 15 hours, releasing drug gradually for absorption by the proximal small intestine. The starting dose is 300 mg/day once daily and increased over 2 weeks to a target dose of 1800 mg/day. Three multicenter, randomized, controlled double-blind studies have been reported either shortly before publication of the most recent guidelines or after publication. One study of 452 patients randomized to once daily gastroretentive gabapentin or placebo demonstrated a statistically significant

reduction in mean change in NPRS scores from baseline and in percentage change from baseline to the final week of the treatment period (Week 10).[22] A second study of 407 randomized subjects showed statistically significant improvements in a range of secondary endpoints (average pain on the Neuropathic Pain Score; worst pain, average pain, and current pain on the Brief Pain Inventory). Using last observation carried forward (LOCF) imputation method, which was the imputation method used in the high-concentration topical capsaicin studies, once daily gastroretentive gabapentin also showed a statistically significant improvement in average daily pain score (NPRS) over 10 weeks of treatment. However, on the primary endpoint using the prespecified baseline observation carried forward (BOCF) imputation method, once daily gastroretentive gabapentin (1800 mg/day) was no better than placebo over 10 weeks of treatment.[23] A third study[24] also failed to show a statistically significant difference vs. placebo over 4 weeks of treatment, 2 weeks of which were the titration phase and 2 weeks of which were at full dose. All of these studies used a conservative imputation approach to missing data (BOCF versus the less conservative LOCF). The BOCF method will typically underestimate efficacy compared with LOCF; for patients who don't complete the study, the baseline scores (pretreatment) are carried forward. With LOCF, the last available score before dropout is carried forward (and thus usually includes scores after some interval of treatment).

Based on the available evidence, gastroretentive gabapentin meets the standard of first-line therapy in the EFNS guidelines (one rigorous RCT needed). Whether it meets the standard of first-line therapy in the NeuPSIG guidelines (multiple RCTs needed) is a matter of interpretation. Unlike the high-concentration topical capsaicin studies, each of the three gastroretentive gabapentin studies used a conservative imputation method for each primary efficacy analysis, and one of the failed studies showed clear separation from placebo when data were analyzed using the LOCF imputation method. Based on the available evidence and other features of gastroretentive gabapentin (such as dosing convenience, pharmacokinetics), we believe it can be considered a first-line option for PHN in certain clinical situations. When administered with an evening meal, peak dose occurs in the early morning (approximately 3 AM), when patients are sleeping. This may account for the observed improved tolerability of gastroretentive gabapentin (lower rate of dizziness and sedation) relative to published reports of gabapentin IR and pregabalin.

Gabapentin enacarbil

Gabapentin enacarbil is a twice daily extended-release formulation of gabapentin, specifically formulated as a prodrug. It is currently FDA approved for restless leg syndrome and PHN. A randomized, double-blind study of 115 patients with PHN showed superior pain relief with gabapentin enacarbil versus placebo as assessed by mean change from baseline in pain scores and 30% response rate.[25] This study consisted of a 4-day titration phase with gabapentin immediate release, a 7 day run-in phase with gabapentin immediate release 1800 mg, followed by randomization to either gabapentin enacarbil 1200 mg BID or placebo, which subjects received for 2 weeks. Data imputation for subjects who did not complete the double-blind treatment consisted of the mean daily pain scores from the preceding 7 days. The primary efficacy endpoint was change in weekly pain score from baseline to the final week on double-blind treatment.

Limited published data are available on this product, and the short duration of this trial precludes any assessment of this product's long-term efficacy. However, a 12-week efficacy study described in the product label showed efficacy at all doses tested (up to 3600 mg/day), but 2400 mg/day and 3600 mg/day showed no greater efficacy than 1200 mg/day, and adverse effects were more pronounced at higher doses. The starting dose of gabapentin enacarbil is 600 mg in the morning for 3 days; on day 4, dose should be increased to 600 mg twice daily. Though early evidence demonstrates efficacy with an increasing dose-dependent side effect profile, twice daily dosing provides a clear disadvantage versus once daily dosing of gastroretentive gabapentin and titration above 1200 mg/day is not indicated. The lack of a published randomized controlled trial of significant duration is a limitation and precludes a full evaluation of this product's place in treatment.

Pregabalin combination therapeutic approaches

Several recent studies have evaluated the use of pregabalin in combination with lidocaine plaster,[26,27]

oxycodone,[28] or transcutaneous electrical nerve stimulation (TENS).[29] Rehm and colleagues and Baron and colleagues assessed the combination of topical lidocaine and pregabalin but no data on statistical significance of the findings were reported. Zin and colleagues found that the addition of a fixed-dose of oxycodone 10 mg did not add to the efficacy of pregabalin, but given that opioids are typically titrated to effect, the fixed-dose of oxycodone may have been too low.[28] A study comparing the use of pregabalin with TENS showed that the addition of TENS to pregabalin 300 or 600 mg/day resulted, after 4 weeks of treatment, in a statistically significant improvement in pain assessed using a visual analog scale,[29] compared with pregabalin alone.

8. What are key considerations in choosing postherpetic neuralgia treatments?

Efficacy is a critical factor in treatment selection, but several other factors must be considered when selecting a treatment for a person with PHN. These include:

Tolerability

Common adverse effects associated with first- and second-line options for PHN are shown in Table 1.3. A key consideration for therapeutic success is the ability of the patient to tolerate the therapy long-term, a parameter that is specifically required of class I evidence only in the PHN-specific guidelines published.[6] For a study to be rated as class I by AAN, at least 80% of subjects must complete the study.[30] Those options associated with the potential for significant drowsiness and somnolence pose a challenge for patients, in particular the elderly. Alpha-2 delta ligands are associated with dizziness and somnolence in 10%–20% of patients and should therefore be used cautiously in patients with gait or balance problems. CNS effects of gabapentin IR, gastroretentive gabapentin, gabapentin enacarbil, and pregabalin are shown in Table 1.4. Given the fact that dizziness and somnolence are common with all first- and second-line systemic medications (except TCAs) for PHN, even an incremental reduction in these adverse effects may be significant. Picking such an agent is difficult in the absence of head-to-head studies but the reader should review Table 1.4 for guidance. Tramadol is associated with seizure risk if given alone or if given with selective serotonin reuptake inhibitors (SSRIs), TCAs, or other opioids. Although a rare side effect, it is also associated with an increased risk of serotonin syndrome if given with SSRIs, selective norepinephrine reuptake inhibitors (SNRIs), TCAs, or monoamine oxidase inhibitors (MAOIs). Anticholinergic effects are common with TCAs, but may be less

Table 1.3. Common adverse effects

Drug class	Key adverse effects
TCAs*	Cardiac toxicity, postural hypotension, urinary retention, angle-closure glaucoma, dry mouth, constipation, sweating
Gabapentin IR	Dizziness, somnolence, ataxia, fatigue, weight gain, dry mouth, peripheral edema
Gastroretentive gabapentin	Dizziness, somnolence, ataxia, fatigue, weight gain, dry mouth, peripheral edema
Gabapentin enacarbil	Dizziness, somnolence, fatigue/asthenia, peripheral edema
Pregabalin	Dizziness, somnolence, ataxia, fatigue, weight gain, dry mouth, peripheral edema
Opioids	Constipation, nausea, somnolence, dizziness, pruritis
Tramadol	Dizziness, nausea, constipation, somnolence, flushing, pruritis, insomnia, asthenia Seizure risk at high doses and when given with SSRIs, TCAs, opioids Serotonin syndrome risk when given with SSRIs, SNRIs, TCAs, MAOIs, and triptans

* Secondary amines (nortriptyline and desipramine) are considered by the NeuPSIG guidelines as better tolerated than tertiary amines (amitriptyline, imitriptyline).
Abbreviations: SSRI, selective serotonin reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

Table 1.4. CNS effects of alpha2-delta ligands

		% of AE with Alpha-2 Delta Ligands (% of AE with Placebo)		
	Gabapentin IR*	Gastroretentive gabapentin†	Gabapentin enacarbil‡	Pregabalin§
Dizziness	28.0 (7.5)	10.9 (2.2)	17.0 (15.0)	21.0[5]
Somnolence	21.4 (5.3)	4.5 (2.7)	10[8]	12.0[3]
Lethargy	NR	1.1 (0.3)	NR	NR
Fatigue/asthenia	NR	NR	6.0[1]	NR
Ataxia	3.3 (0)	NR	NR	3[1]
Vertigo	NR	NR	NR	3[1]
Confusion	NR	NR	NR	2[1]
Thinking abnormal	2.7 (0)	NR	NR	2 (0)
Abnormal gait	1.5 (0)	NR	NR	1 (0)
Incoordination	1.5 (0)	NR	NR	2 (0)
Amnesia	1.2 (0)	NR	NR	1 (0)
Hypesthesia	1.2 (0)	NR	NR	NR

* Neurontin (gabapentin) Package Insert
† Gralise (gabapentin) Package Insert
‡ Horizant (gabapentin) Package Insert. Rates are based on 1200 mg/day. At higher doses, dizziness was 26% with 2400 mg/day and 30% with 3600 mg/day.
§ Lyrica (pregabalin) Package Insert.
Abbreviations: AE, adverse event; NR, not reported.

common with the secondary amines (nortriptyline and desipramine) compared to the tertiary amines (amitriptyline and imitriptyline). Opioids' adverse effects include dizziness, somnolence, constipation, hypogonadism, and nausea and are associated with the risk of misuse and abuse. Although from an analgesic viewpoint, opioids are generally at least as effective as other drugs for PHN, they are typically not recommended as first line mainly because of their adverse effect profile as well as risk of abuse and the need to screen patients for risk of abuse, monitor potential abuse, and intervene if abuse is suspected. Both topical options (capsaicin and lidocaine) have negligible systemic adverse effects and thus can be very useful for patients on multiple medications or who cannot tolerate systemic medications.

Dosing and onset of analgesia

Prescriber knowledge of dosing of available drug therapies is critical for success (Table 1.5). To minimize adverse effects, a slow titration phase is required for TCAs, gabapentin IR, and pregabalin. In contrast, gastroretentive gabapentin can be titrated over 2 weeks up to 1800 mg/day, and gabapentin enacarbil over 1 week up to 1200 mg/day. Onset of efficacy for these agents may be delayed, but if the patient is tolerating these drugs well, the provider and patient should make every effort to complete the titration phase and not terminate early. Frequency of dosing is a major contributor to adherence with chronic use. There is no titration required for the 5% lidocaine patch nor the 8% capsaicin patch. Although few studies have assessed dosing frequency and adherence in chronic pain, in several other therapeutic areas adherence increases with decreasing dosing frequency.[31] Ideally, TID medications should be avoided in favor of medications with BID or QD dosing, especially in patients on multiple medications. In this regard, medications such as topical capsaicin (8%) (applied once every 3 months), the topical lidocaine patch (3 patches applied 12 hours daily), gastroretentive gabapentin (once daily), gabapentin enacarbil (twice daily), the TCAs (once daily or given in two divided doses per day), and some extended-release opioid formulations are more attractive. Gabapentin IR is given three times daily, and pregabalin two to three times daily.

Table 1.5. Dosing and onset considerations*

Drug class	Dosing	Duration of adequate trial
TCAs	Start at 25 mg at bedtime Increase 25 mg/d every 3–7 days	6–8 weeks with at least 2 weeks at maximum tolerated dosage
Gabapentin IR	Start at 100–300 mg at bedtime or 100–300 mg 3 times daily Increase by 100–300 mg 3 times daily every 1–7 d as tolerated	3–8 weeks for titration plus 2 weeks at maximum dose
Gastroretentive gabapentin	Take with evening meal Start at 300 mg/d Increase dose to 600 mg/d on day 2, 900 mg/d on days 3–6, 1200 mg/d on days 7–10, 1500 mg/d on days 11–14, and 1800 mg/d on day 15	Not defined
Gabapentin enacarbil	Start at 600 mg in the morning for 3 days Increase to 600 mg BID beginning on day 4	Not defined
Pregabalin	Start at 50 mg 3 times daily or 75 mg twice daily as tolerated. Increase to 300 mg/d after 3–7 d, then by 150 mg/d every 3–7 d as tolerated	4 weeks
Topical lidocaine	Maximum of three patches daily for a maximum of 12 hours	3 weeks
Topical capsaicin (8%)	1 patch applied for 60 minutes every 3 months	Not defined
Opioids	Start at 10–15 mg morphine or morphine equivalents every 4 hours as needed After 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	4–6 weeks
Tramadol	Start at 50 mg once or twice daily Increase by 50–100 mg/d in divided doses every 3–7 d as tolerated	4 weeks

* Modified from[7] (Table 2).

Are there challenging subsets of patients and guideline gaps in subpopulations of patients with postherpetic neuralgia?

The older patient

The PHN patient is typically older, has several comorbidities, and takes multiple medications resulting in special considerations and gaps in treatment considerations (Table 1.6). Approximately 20% of people 65 years of age or older are taking 5 or more drugs.[32] Of the 10 most commonly administered medications given to the elderly, 6 of them (hydrochlorothiazide, lisinopril, metoprolol, atenolol, amlodipine, and furosemide) cause drowsiness, dizziness, or somnolence.[33] Thirty percent of hospitalizations are associated with drug-related problems or adverse effects.[34] This population is particularly sensitive to adverse effects of medications, and it is here where treatment selection becomes complicated.

In addition to a standard pain work-up, special attention should be paid to assessing the older patient's physical function. Range of motion testing, gait, and balance testing should be considered, and if deficits are found, drugs with a higher risk of dizziness and somnolence should be avoided or used with caution. Because some side effects can be minimized or avoided with slow titration, if the patient with gait or balance problems is a candidate for a drug causing significant sedation or drowsiness, a low starting dose and slow titration schedule may alleviate some of these side effects. Older patients have decreased renal and hepatic function, altered drug distribution, and decreased blood volume, which can affect drug metabolism and tolerability. Glomerular filtration rate decreases by about 0.75 to 0.9 ml/min per year after the age of 30–40 years. By the age of 80, glomerular filtration rate may be two-thirds that of a

Table 1.6. Guideline gaps

	Special populations					
	Elderly	**Depression**	**Anxiety**	**Renal/ hepatic impairment**	**Cardiovascular comorbidities**	**History of substance abuse**
NeuPSIG	Topical lidocaine's lack of systemic adverse effects and drug interactions make this product advantageous in older patients	NA	NA	Dose reduction required for gabapentin and pregabalin in pts with renal insufficiency	Prescribe TCAs with caution in pts with ischemic heart disease or ventricular conduction abnormalities; limit dosages to 100 mg/d when possible; obtain screening ECG	Risk of abuse of tramadol seems considerably less than that with strong opioids Avoid strong opioids as 1st-line therapy due to risk of abuse/misuse If opioids used, monitor for signs of abuse
EFNS	Topical lidocaine, with its excellent tolerability, may be considered 1st-line in the elderly	NA	NA	NA	NA	NA
CPS	Topical lidocaine is a good 2nd-line analgesic for elderly	NA	NA	NA	TCAs are "relatively" contraindicated	NA
AAN	NA	NA	NA	NA	NA	NA
AGS	Start with lower doses of most drugs Older pts rarely tolerate TCA doses > 75–100 mg/d Monitor sedation, ataxia, and edema with alpha-2 delta ligands Opioids can be an effective option in properly selected and monitored patients					

NA = not addressed.

healthy 20- to 30-year-old.[35] Elderly patients are also more sensitive to opioids and benzodiazepines.[36]

The American Geriatrics Society (AGS) notes that the elderly and patients with multiple comorbidities are rarely studied in randomized controlled trials, so most recommendations are made based on highly selected and younger populations. The AGS recommends a patient-centered approach, which begins with understanding the patient's primary concern and treatment goals.[37] AGS also provides the following recommendations:

- Pain is underreported in the older patient so clinicians must make an effort to assess it, even in patients with cognitive impairment. Special pain assessments for patients with cognitive impairment exist, a summary of which has been described in an expert consensus statement.[30]
- Because of age-related decrements in drug metabolism and clearance, starting doses should