Chronic pain following surgery is a major complication affecting between 10% and 30% of patients following a wide variety of surgeries. The hand and upper limb are especially susceptible to postsurgical pain because of the rich innervation and unique demands of the upper extremity. Neuropathic pain after hand/upper limb surgery is likely produced through at least 3 potential mechanisms: (1) transection of cutaneous branches during skin incision with neuroma formation in the skin scar; (2) adherence of postsurgical scar tissue to nerves either in the skin or deeper without transection of these nerves (exacerbated by the postoperative immobilization often required for bone healing); and (3) entrapment of nerve branches remote from the skin incision. This entrapment can be proximal to the surgical insult caused by edema tracking along the nerve course and resulting in compression at sites where surrounding tissue is noncompliant. Another factor that puts the upper limb at risk for neuropathic pain is that few parts of the body are as mobile, or have the degree of excursion, as the nerves traveling from the cervical spine to the fingertips. These nerves cross multiple joint lines but, after trauma, nerves can become tethered in immobile cutaneous scars surrounded by keratinocytes secreting chemokines and growth factors that promote painful neuromas. Beyond the physical characteristics of the upper limb, many central and peripheral mechanisms also likely contribute to the development of chronic pain and undermine the results of a technically perfect surgery.

Many physicians think that neuropathic pain is tingling or electrical and therefore complaints of sore, heavy, dull, or throbbing pain are considered not neuropathic in nature. However, surveys of patients with neuropathic pain, such as spinal cord injury pain, acute herpes zoster, postherpetic neuralgia, and diabetic neuropathy, found that this pain was often described as a dull throbbing or heavy pain. Therefore the most important point in better treating the chronic pain after surgery is to recognize that this pain is more frequently than expected neuropathic in origin. There are some data suggesting that some of the medications that are frequently used to treat neuropathic pain work best for those people whose pain is not described in classic neuropathic...
terms but who describe their pain as sore, dull, or heavy.17–19

Similarly, it is my own personal experience that cutaneous scar neuromas are invariably described by patients as a diffuse and deep pain. Therefore, no patient with chronic postsurgical pain can dissuade me from injecting their cutaneous scar with local anesthetic. For me, the only convincing evidence that a scar neuroma is not present and a major source of the patient’s chronic pain is failure to have temporary profound analgesia in response to a scar injection with local anesthetic. Scar neuroma is an underexplored and underreported area of investigation in the literature on chronic postsurgical pain.

This article describes the basics of pharmacologic treatment of neuropathic pain (the most common type of chronic pain after surgery). This article is intended for upper extremity surgeons and allied practitioners who are not pain specialist but for whom a better understanding of how to treat nerve pain will be of great benefit.

GENERAL TENETS

1. Do not be in a hurry. The medications that most successfully reduce neuropathic pain and have the most durable analgesic effects all require some patience to be maximally successful. An expectation that they will work as quickly as commonly used pain relievers (opioid medications: eg, Vicodin, codeine) results in profound disappointment for both provider and patient. More importantly, impatience may cause you and your patient to prematurely put aside one of the few medications that can produce long-term profound pain relief. An expectation that neuropathic pain medicines will work on the time scales patients have come to expect from their previous exposure to opioids will cause a drug that might have been successful to be rejected. In addition to differing in their time to effectiveness, medications used for neuropathic chronic postsurgical pain also seem to have a threshold effect not commonly seen with the opioids. A patient may take a small quantity of an opioid and experience minor relief and know from experience that if they take more it is likely to provide greater relief. In contrast, many of the antidepressants and anticonvulsants used to manage neuropathic pain (henceforth referred to as antineuropathics) seem to have a threshold effect; a patient might feel no relief at 25 mg or 50 mg of nortriptyline, and then at 75 mg start to feel relief, and then at 150 mg feel profound relief. Patients’ initial experience of the drug may therefore not reflect their subsequent experience with a higher dose.

2. Antineuropathics should be started at ineffective doses. When started at an effective doses antineuropathic medications often create side effects. These side effects can largely be avoided by slow titration from a low dose, which allows patients to accommodate to the medication effects. For example, duloxetine creates nausea in as many as 25% of patients when started an effective dose of 60 mg. However, if started at the ineffective dose of 20 mg a day, and then increasing the dose by 20 mg weekly up to 60 mg, then nausea becomes an infrequent side effect.21–23 It is generally difficult to talk someone into retrying a drug that they are convinced makes them vomit (or be dopey and so forth), so it is better to start at a low, explicitly ineffective dose and gradually titrate up to an effective dose. I tell patients that I am going to give them a certain drug at a dose that does not work. We use the first few weeks not to help with the pain but just to get the patient’s body used to this medication, then after a few weeks we start to explore doses that might help. Failure to have this kind of conversation with the patient results in loss of confidence in the physician and the medication when the medication fails to improve pain in the first few days.

3. There is some evidence that even though these drugs may exert some effect immediately at any given dose, the degree of pain relief may build substantially over the first few weeks of treatment.22,23

4. Unlike penicillin, for which there is a clear correct dose, with all of these antineuropathic medications doses have to be tailored to the individual. Given current technology it is impossible to know what dose may be too much for one person and not enough for another. Thus you have to test a given dose in a given person and then slowly change the dose to see the degree of side effects and the degree of pain relief. So the policy is:
   a. Start low (start at a dose that you are confident will not create side effects; usually a dose too low to be effective)
   b. Go slow (increase the dose by small increments every few days or each week so that you plan to reach the target dose in 1 to 2 months)
   c. But go! (when you start one of these medications do not just pick a low dose and leave it there, or decide that it does not work just because it is not having an effect at that low dose)
These medications should generally be slowly titrated up until:

i. The patient is getting significant pain relief, or

ii. The patient is reaching a dose defined by the medical literature to include some risk of sudden significant hazard (eg, desipramine at >200 mg/day is feared to cause an arrhythmia), or

iii. The patient is having dose-limiting side effects (eg, gabapentin is making a patient feel too sleepy or too nauseated)

5. Invest a small amount of effort into obtaining or making some dose titration schedules. It is cumbersome to write out dose titration schedules and this prevents people from gradually escalating the dose of medications (Tables 1 and 2). When clinicians write prescriptions like this: "Desipramine 25 mg; 1 to 6 tabs po qam; start 1 tab and increase according to dose schedule until taking 6 tabs po qam; dispense 180; 3 refills" they markedly reduce the problem of having the pharmacy dispense too few pills or having the insurance company cover too few pills.

6. Only change 1 thing at a time. People in pain want to get out of pain immediately and clinicians can be tempted to try multiple things at the same time. I am convinced that this strategy is always wrong. With this strategy, when the patient experiences side effects, neither patient nor physician knows which intervention is causing the side effect. Equally importantly, if intervention works, neither patient nor physician knows what is working. In both settings, patient and physician rely on previous beliefs about the medications and interventions to explain the results, resulting in a confirmation bias that may reinforce incorrect beliefs. For both physicians and patients, slowly learning what works and what does not, and why things do not work (eg, lack of efficacy vs overwhelming side effects), is important to eventually achieving success. Perhaps more importantly, if a physician only changes 1 thing at a time and then sees the result, and that experience is repeated by 100 or 1000 patients, then that physician develops much more accurate clinical acumen. Thus, the one-thing-at-a-time approach is just as important for becoming a better physician over time as it is for helping patients learn what really works and what are the trade-offs for that analgesia.

7. Make the patient commit to the process. In general, taking these medications one day

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**Table 1**

<table>
<thead>
<tr>
<th>Dosing schedule for desipramine (Norpramin 25 mg; also available as 10, 50, 75, 100, and 150 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 1</strong></td>
</tr>
<tr>
<td>Day number</td>
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<tr>
<td>Morning</td>
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<tr>
<td><strong>Week 2</strong></td>
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<tr>
<td><strong>Week 3</strong></td>
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<tr>
<td><strong>Week 4</strong></td>
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<td>Morning</td>
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<td><strong>Week 5</strong></td>
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<td>Day number</td>
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<tr>
<td>Morning</td>
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</tbody>
</table>

#180 tablets dispersed (at 6 tabs by mouth every day).
If complete pain relief occurs, continue at that dose without further increases and call the pain clinic.
If concerning side effects occur, return to previous dose and call the pain clinic. Most side effects resolve with time, at which point the dose can again be escalated.

Potential side effects: dizziness, somnolence, fatigue, nausea, difficulty urinating, constipation, sexual dysfunction, arrhythmias, dry mouth, blurred vision, increased eye pressure in glaucoma, rash.

a Continue 6 tablets a day and call pain clinic to report results. We often do not see results until doses of 60 to 100 mg have been reached. Maximum initial dose is 150 mg/d.
and skipping them the next because of frustration makes the patient feel awful, so patients should commit to giving the medication a 6-week trial, or decide that they are not ready. The anticonvulsants and antidepressants used for nerve pain do not work when used haphazardly and patients become falsely educated that these medications do not work when in reality they are not working because of incorrect administration.

Neuropathic pain is a chronic condition that cannot always be fixed, and it is therefore important to introduce early the concept that neuropathic pain represents a chronic condition, like increased blood pressure, diabetes, or asthma, that requires long-term management rather than a fix. This message can be difficult to deliver, especially if the provider is the one who was operating at the time the chronic postsurgical pain began. Surgeons need to feel comfortable with the idea that the pain was caused by the surgery but it is almost certainly not the fault of the surgeon’s technique or patient selection. Acceptance of the chronic disease paradigm at the initiation of treatment helps create a shared sense of

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Dosing schedule for gabapentin (Neurontin 300 mg)</td>
</tr>
</tbody>
</table>

| Week 1 | |
|---|---|---|---|---|---|---|
| Day number | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|Morning | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
|Noon | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|Evening | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

| Week 2 | |
|---|---|---|---|---|---|---|---|
| Day number | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|Morning | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|Noon | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|Evening | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

| Week 3 | |
|---|---|---|---|---|---|---|---|
| Day number | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|Morning | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
|Noon | 1 | 1 | 1 | 2 | 2 | 2 | 2 |
|Evening | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

| Week 4 | |
|---|---|---|---|---|---|---|---|
| Day number | 22 | 23 | 24 | 25 | 26 | 28 | 28 |
|Morning | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|Noon | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
|Evening | 2 | 2 | 2 | 3 | 3 | 3 | 3 |

| Week 5 | |
|---|---|---|---|---|---|---|---|
| Day number | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
|Morning | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
|Noon | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
|Evening | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

| Week 6 | |
|---|---|---|---|---|---|---|
| Day number | 36 | 37 | 38 | 39 | 40 | 41 | 42 |
|Morning | 3 | 3 | 3 | 3 | 3 | 3 | 4 |
|Noon | 3 | 3 | 4 | 4 | 4 | 4 | 4 |
|Evening | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

#360 tablets dispersed (at 4 tablets by mouth 3 times a day).
Potential side effects: dizziness, somnolence, fatigue, gastrointestinal upset, ataxia, tremor, abnormal vision or gait, abdominal pain, nystagmus, rash, headache, cognitive effect.
If during the increasing dosing schedule the patient develops any of these side effects, the patient should stop increasing the dose of medicine.
If the medicine has been providing pain relief, return to the dose that was taken before the occurrence of side effects.
realistic goals of treatment. I find it helpful to tell patients specifically which nerve is injured and that I cannot make the nerve the way it was before surgery. Every surgery cuts nerves because there are nerves in every part of the skin. In addition, I counsel that it is not known why most people only develop an area of numbness after surgery but a minority of patients develops nerve pain. I then reassure them that although I cannot fix their problem, I can help them have substantially less pain at the expense of having to take medications indefinitely (as for high blood pressure).

In addition, because chronic pain is also associated with depression and anxiety, it is important that comorbid psychological disorders be treated aggressively. For this reason, it is often preferable to initiate treatment of neuropathic pain with a medication that addresses both pain and comorbid depression and anxiety. There are several agents that have activity in both the pain and psychological realms, including the tricyclic antidepressants (TCAs) and duloxetine.

There are few direct head-to-head trials of medications commonly used to treat neuropathic pain that would help specifically guide choice of one particular agent by efficacy. Among antidepressant drugs used for neuropathic pain the choice is between duloxetine (marketed as an extended release formulation under the brand name Cymbalta in the United States and more recently as a generic extended-release formulation as well) and the TCAs (amitriptyline, nortriptyline, and desipramine). The TCAs have been evaluated as treatments for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia in trials that often used a crossover design, and had sample sizes considerably smaller than more recent randomized controlled trials of duloxetine and pregabalin. To try to compare interventions, the Canadian Pain Society and others have used data based on number needed to treat (NNT) to compare different agents used for nerve pain. The estimated NNT for the tricyclics in neuropathic pain is between 2 and 3. In contrast, the NNT for duloxetine based on duloxetine’s 3 randomized controlled trials in diabetic neuropathy is closer to 5. Other systematic reviews of the literature comparing the effectiveness of TCAs with that of gabapentin suggest the superiority of TCAs for treating neuropathic pain.

**TRICYCLIC ANTIDEPRESSANTS**

TCAs were the first medications that proved effective for neuropathic pain in placebo-controlled trials. More than 17 placebo-controlled trials have shown the efficacy of TCAs for the treatment of neuropathic pain. The NNT for the TCAs is close to 2, suggesting a higher percentage of people may respond to TCAs than other medications. The primary problem with the use of TCAs is their adverse effect profile. TCAs must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, and the elderly. TCAs are not appropriate for patients at risk of overdose because of their well-described lethality in overdose. TCAs should also generally be avoided in patients currently being treated with selective serotonin reuptake inhibitors (SSRIs), for both pharmacokinetic and pharmacodynamic reasons. SSRIs inhibit the cytochrome P450 2D6 enzyme, which normally breaks down TCAs. Thus people taking SSRIs and TCAs at the same time are at risk of having marked increases in their TCA levels. Furthermore, the shared serotonin reuptake inhibition puts patients at risk of serotonin syndrome. Despite this, in rare monitored settings, the concurrent use of these medications can sometimes be accomplished safely.

Nortriptyline and desipramine are two of the tricyclics with the lowest affinity for the muscarinic cholinergic and histaminic receptors, and they therefore cause less sedation, constipation, and dry mouth than the more commonly prescribed amitriptyline (Elavil). Desipramine in particular has the greatest noradrenergic profile and least antimuscarinic and antihistaminic profile of all the drugs in this class, making it particularly attractive among tricyclics. Desipramine is usually slightly activating rather than sedating, and, in contrast with nortriptyline, is therefore better given in the morning than at night. Occasionally desipramine leads to difficulty sleeping because of its activating properties. However, perhaps because of its activating properties or its lower antihistaminic and anticholinergic profiles, desipramine does not seem to cause the same problematic weight gain seen with nortriptyline or amitriptyline. In contrast, nortriptyline is mildly sedating and is therefore better given at night.

Patients and practitioners must understand that TCAs have analgesic effects independent of their antidepressant effects. They are effective for relieving pain in people who are not depressed, they occasionally work for pain at doses that are not high enough to treat depression, and they work on time scales much faster for pain than for depression. TCAs such as desipramine should be initiated at a low dose (10–25 mg as a single dose) and then titrated every 3 to 7 days by 10 to 25 mg/day as tolerated. Although the analgesic effect of TCAs has been thought to occur at lower dosages than the antidepressant effects, there is evidence that higher doses of TCAs are markedly
more effective than lower doses for the treatment of neuropathic pain.\textsuperscript{29–31} TCAs should generally be titrated to dosages between 75 mg and 200 mg a day to maximize the likelihood of a good response. To ensure safety and to monitor for toxicity, electrocardiograms and blood levels should be checked once a patient reaches 150 mg/day. Blood levels of 500 ng/mL or higher are more likely to be associated with toxicity, with toxicity becoming the likely outcome of blood levels greater than 900 ng/mL. We typically target plasma concentrations between 100 and 300 ng/mL. Monitoring for toxicity is particularly important for desipramine. Desipramine may be the best-tolerated TCA, but, because of its potency, desipramine may also be particularly dangerous when given to patients with cardiac disease, or when taken in an overdose. Drug level monitoring identifies the patients with undesirably high or low plasma levels for appropriate action.\textsuperscript{31}

Different individuals metabolize these medications differently because people can have different activity at the cytochrome P450 2D6 enzyme, the enzyme primarily responsible for digesting TCAs in the liver. Approximately 10% of caucasian have very limited activity at this enzyme, whereas between 20% and 30% of African Americans lack activity at this enzyme. Consequently these individuals with low activity can have very high blood levels when given normal doses of TCAs. In contrast, there is a smaller subset of individuals who are very rapid metabolizers. In these individuals, seemingly appropriate doses yield low blood levels that are ineffective, and following blood levels allows these patients to be identified and targeted for higher doses of TCA treatment.

In elderly patients TCAs may cause balance problems and cognitive impairment. Other adverse effects of TCAs include sedation, dry mouth, constipation, orthostasis, and occasionally weight gain. Weight gain best correlates with antihistaminic properties of the TCAs. Desipramine has markedly lower antihistaminic properties than other TCAs and does not seem to be associated with much, if any, weight gain; a notable problem with amitriptyline and nortriptyline.\textsuperscript{28}

In addition to the higher efficacy of TCAs compared with other agents for neuropathic pain, other reasons to prefer initial treatment of neuropathic pain with TCAs include:

1. Their low cost.
2. Their effectiveness in treating comorbid depression. Comorbid depression occurs in up to 60% of individuals with chronic pain.
3. Once-a-day dosing with a half-life of approximately 23 hours improves ease of use and patient compliance, and therefore efficacy.
4. The ability to measure serum plasma levels and therefore identify patients who might otherwise fail treatment for pharmacokinetic reasons.
5. The wide range of doses available, from 10 mg to 300 mg as a single pill.
6. The reduced likelihood of causing cognitive side effects compared with anticonvulsant medications.

**DULOXETINE AND VENLAFAXINE**

Duloxetine and venlafaxine are selective norepinephrine and serotonin reuptake inhibitors (SNRIs). They therefore share some mechanistic similarities with TCAs, but lack the TCAs blockade of sodium channels and antagonism at alpha1-adrenergic, muscarinic cholinergic, and type 1 histamine receptors. The evidence for SNRI efficacy for neuropathic pain is much better established for duloxetine than for venlafaxine, which has shown mixed results and is not US Food and Drug Administration (FDA) approved for a pain indication, although we have seen patients respond to both.\textsuperscript{22,23} Duloxetine is approved by the FDA to treat the pain associated with diabetic neuropathy. As described earlier, the NNT for duloxetine is perhaps twice as high as for the TCAs,\textsuperscript{26} but duloxetine lacks the cardiac toxicity described for TCAs. We have found that duloxetine is noticeably less effective than TCAs. However, it may be well tolerated by some patients who are even worse candidates for TCAs or gabapentinoids; for example, the elderly. Some elderly patients develop clinically significant orthostatic hypertension with effective doses of duloxetine. Until recently it was only available as the branded drug Cymbalta, but now it is available as a generic sustained-release capsule. When started at a dose effective for nerve pain (60 mg or more) duloxetine causes nausea in at least one-quarter of patients.\textsuperscript{22,32} However, this is easily avoided for most patients by starting at 20 mg/day and gradually escalating the dose to between 60 mg and 120 mg. Cases of fulminant hepatic failure have been reported for duloxetine and its use in patients with hepatic impairment is not recommended.\textsuperscript{33} Patients who abruptly discontinue duloxetine or venlafaxine after spending several months on either medication may become very unhappy and report a variety of bizarre somatic and cognitive symptoms, as well as emotional lability and extreme feelings of despondence.\textsuperscript{34,35} Several of our patients have described feeling electrical zaps throughout their bodies on sudden
cessation of duloxetine. These symptoms have been reported by others as well. These symptoms stop abruptly on reinitiating duloxetine, but may persist for weeks if the patient decides to persist rather than reinitiate the duloxetine.

GABAPENTINOIDS

Gabapentin and pregabalin (collectively termed gabapentinoisods) should be considered first-line treatment of neuropathic pain. These medications have a shared mechanism of action, which seems to involve the modulation of voltage-gated calcium channels existing on presynaptic pain-carrying neurons in the dorsal horn of the spinal cord. It is thought that the action of gabapentin and pregabalin on these voltage-gated calcium channels inhibits the presynaptic release of pronociceptive neurotransmitters such as glutamate and nociceptive peptides. These medications have proven efficacy for the treatment of neuropathic pain arising from diabetic peripheral neuropathy and postherpetic neuralgia. Their use in chronic postsurgical pain stems from an appreciation that chronic postsurgical pain often arises from nerve injury. Studies suggest that the NNT for these medications ranges from 4 to 6.26

The structure of gabapentin is similar to that of an amino acid and, unlike many medications, gabapentin relies on an active transport process for absorption, a process that can be saturated. Consequently the absorption of gabapentin from the duodenum is nonlinear, with progressively lower increments of gabapentin being absorbed as the dose increases. This property provides gabapentin with both a built-in safety mechanism and also a built-in efficacy ceiling because patients can only absorb so much gabapentin at a time. Consequently, to become overmedicated with gabapentin usually requires either some impairment that makes the patient unusually susceptible to the effects of cognitively impairing medications, or alternatively the patient has to have a defect in gabapentin elimination. Gabapentin is normally excreted unchanged by the kidneys so gabapentin can accumulate in patients with renal insufficiency, causing significant cognitive impairment, oversedation, and myoclonus.

Pregabalin (Lyrica) has the same mechanism of action as gabapentin but differs primarily in the pharmacokinetics governing its absorption from the intestines. Pregabalin is not dependent on an active transport process in the duodenum that can be saturated, but is absorbed more diffusely throughout the intestines and has linear pharmacokinetics at clinically relevant doses in humans. Because it has a shared molecular mechanism of action with gabapentin, it is hard to explain the occasional patients who report that they tolerate pregabalin but experienced cognitive side effects with gabapentin. Nonetheless, as a general rule, pregabalin should not be the first drug trialed among patients reporting cognitive side effects from gabapentin, because a better-absorbed version of a drug with the same mechanism of action should not be relied on to result in fewer side effects. However, for that subgroup of patients who are inclined to take a higher dose of gabapentin because of inadequate analgesia, and the absence of dose-limiting side effects, but are unlikely to be able to absorb higher doses of gabapentin (ie, they are taking a dose close to the maximum absorbable amount; roughly 3600 mg/day), switching to pregabalin, or alternatively augmenting with pregabalin, may bypass the dose-limiting bottleneck presented by inadequate duodenal absorption of gabapentin.

COMBINATIONS

There are several high-quality studies of medication combinations for neuropathic pain, but few of the combinations have been replicated. The exception to this is the combination of an opioid plus gabapentin. A recent meta-analysis of 386 subjects from 2 trials showed statistically significant but clinically modest superiority of gabapentin when combined with an opioid compared with gabapentin alone. A well-done but small study of the combination of nortriptyline and gabapentin evaluated either drug versus the combination of both drugs.

The study was a double-blind, double-dummy, crossover trial of patients with neuropathic pain who were randomized in a 1:1:1 ratio to gabapentin, nortriptyline, or the combination. Each group was then crossed over to experience each of the other 2 groups. Overall the combination was statistically significantly more effective than either drug alone. This finding in the setting of a small sample size suggests an effect size that is large and that is likely to be clinically meaningful as well. Our own experience is in agreement with these findings. In addition, although these results were obtained in patients with either diabetic neuropathy or postherpetic neuralgia, our own experience suggests that the same agents and combinations seem to be effective in the setting of neuropathic pain caused by postsurgical traumatic nerve injury. In practice, most patients benefit from a combination of medications but the scientific basis of this approach remains limited, with few data to suggest improved efficacy or reduced side effects.
OPIOIDS

Several different opioids have been examined in randomized controlled trials for the treatment of neuropathic pain conditions, including painful diabetic neuropathy, postherpetic neuralgia, sciatica, postamputation pain, and spinal cord injury pain. Overall, these trials seem to support the belief that opioids confer a moderate improvement in pain as well as an improvement in function in patients with neuropathic pain. However, most of the studies are limited by having a short duration. This limitation is particularly problematic because, unlike the antidepressants and anticonvulsants, opioid use results in a greater degree of tolerance, so although it is clear that opioids are helpful when first initiated for neuropathic pain, it is less clear that opioids remain effective for neuropathic pain over time. Furthermore, the adverse side effects of opioids, and in particular the increasing levels of prescription opioid misuse that has paralleled use results in increased availability of prescription opioids, have left many prescribers wondering whether the benefits are worth the costs.

LAMOTRIGINE

Lamotrigine (Lamictal) has had positive results treating neuropathic pain related to human immunodeficiency virus–induced neuropathy, trigeminal neuralgia, and central pain. Two large clinical trials in diabetic neuropathy showed a nonsignificant trend toward a positive effect (P = .07). Overall, the data suggest that lamotrigine may be helpful for some people with neuropathic pain but likely has an effect size smaller than that of the gabapentinoids, TCAs, and duloxetine. Lamotrigine is thought to reduce neuropathic pain through several mechanisms, including sodium channel blockade. In addition, lamotrigine has some serious issues that make it challenging for routine treatment. One in 10 people develops a rash, most commonly in children, patients taking valproic acid or carbamazepine, and those increasing the dose of lamotrigine by more than 25 mg every 2 weeks. The occurrence of this rash with more rapid dose escalation mandates a prolonged period of time between starting lamotrigine and achieving what can be an effective therapeutic dose (typically around 100 mg twice a day). Furthermore, roughly 1 in 1000 people develop a Stevens-Johnson–type syndrome, the potential for which necessitates the cessation of treatment during the occurrence of the much more common rash of a non–Stevens-Johnson type. In contrast, lamotrigine is generally well tolerated with a lower incidence of significant weight gain or cognitive dysfunction compared with gabapentin or pregabalin.

TOPIRAMATE

Topiramate is a second-generation antiepileptic medication that has shown significant efficacy in a variety of headache syndromes as well as in certain seizure disorders. It has several purported mechanisms of action, including sodium channel blockade, GABAergic effects, and carbonic anhydrase inhibition. Early studies of topiramate seemed to show promise for neuropathic pain and 1 large randomized controlled trial showed topiramate to be superior to placebo in reducing the pain among patients with painful diabetic peripheral neuropathy. A follow-on open-label extension also seemed to support the efficacy and sustained pain relief of topiramate for neuropathic pain. However, another group of 3 randomized controlled trials of topiramate for diabetic peripheral neuropathy failed to show a statistically significant effect for topiramate treatment. These studies have been criticized for methodological flaws that might have contributed to a failure to find a real treatment effect of topiramate. These methodological flaws included enrollment of patients whose pain was not particularly severe with a possible floor effect; permission during the study for patients to use opioid analgesics as rescue medication; and a failure to specifically reference lower extremity pain when inquiring about pain and pain relief related to study medication. Note that in the large randomized, placebo-controlled trial that did find a clinically meaningful effect of topiramate to reduce neuropathic pain, these methodological issues were not involved. This randomized, placebo-controlled, multicenter, 12-week study included 323 subjects with pain greater than a 4 out of 10 on a visual analog scale. Fifty percent of patients treated with topiramate experienced a clinically meaningful reduction in pain (defined as 30% or greater reduction in pain on a visual analog score) compared with 34% of placebo-treated subjects (P = .004). Topiramate also improved sleep and reduced worst pain intensity. Unlike most of the drugs that are used for nerve pain, topiramate seems to induce weight loss, and resulted in an average 2.6-kg weight loss over 12 weeks among patients with painful diabetic neuropathy. In our practice, few patients seem to have profound relief with Topamax. However, for the minority of patients who do achieve relief, the relief is often significant. Among these patients, the doses at which relief occurs tend to be in the higher dose ranges; often as high as 400 to 600 mg/day. In contrast, an open-label
26-week study to assess the long-term safety and effectiveness of topiramate among patients with painful diabetic peripheral neuropathy evaluated 205 subjects taking doses up to 600 mg/day and concluded that pain relief was effective and durable. This study suggested that as many as 40% of patients discontinue topiramate. Patients most frequently discontinue because of adverse effects, including cognitive impairment, sedation, lack of appetite, paresthesia, and gastrointestinal upset. We have also rarely seen patients discontinue this medication despite efficacy because of progressive hair thinning. In addition, likely because of its carbonic anhydrase activity, topiramate is associated with an increased incidence of nephrolithiasis. Clinicians familiar with topiramate (marketed in the United States as Topamax) jokingly refer to it as Dopamax because of the sedation. Nonetheless, a small minority of patients seem to be impervious to the cognitive side effects of topiramate and tolerate it at fairly high doses with corresponding pain relief. Patient acceptance of topiramate is often high in the office when patients hear that it may induce weight loss, but enthusiasm wanes quickly when cognitive side effects occur. In addition, female patients should be advised that topiramate may reduce the effectiveness of oral contraceptive pills.

**TOPICAL MEDICATIONS**

**Lidocaine**

Lidoderm is a 5% lidocaine patch that won approval based on its effectiveness in postherpetic neuralgia. It seems to work locally because systemic levels are negligible, and systemic side effects are virtually nonexistent. It was hoped that it would be effective in particular for people with cutaneous nerve injuries such as scar neuromas, a common affliction following upper extremity and hand surgery. However, our experience using topical lidocaine gels or the Lidoderm patch for topical treatment of postsurgical cutaneous nerve injuries has been generally disappointing. We have seen some rare patients who report the Lidoderm patch to be helpful, but these patients are the exception rather than the rule. Furthermore, it is often difficult to get Lidoderm patches covered for conditions other than postherpetic neuralgia. For this reason we often prescribe a small quantity of patches to patients with postsurgical cutaneous nerve injuries and inform patients that they have to pay for it themselves initially. We then try to get it approved for the much smaller number of patients who report to us that they find it useful. However, given the unique safety and virtual absence of systemic side effects, it is hard to argue against a trial of topical lidocaine in patients with cutaneous nerve injuries.

**Capsaicin**

Topical capsaicin, the active ingredient in hot chili peppers, seems to help some patients with postherpetic neuralgia. Although capsaicin initially causes increased pain by activating sensory nerve fibers in the skin, repeated persistent application of over-the-counter-strength capsaicin (less than 1%) causes desensitization and pain relief with some long-lasting but temporary regression of pain fibers from the skin. More recently, the approval of a high-dose capsaicin patch (8%) has allowed some patients to get persistent relief from a single application. There is at least 1 case report of complex regional pain syndrome (CRPS) symptoms getting worse following application of capsaicin patch. Therefore, use of the high-dose capsaicin patch in patients who have developed CRPS following hand surgery should be approached with caution.

**CONCLUSION**

The treatment of pain is a complex process that requires a team approach. This article provides an overview of the pharmaceutical treatments available. One of the goals is to give providers treating upper extremity disorders more tools to treat their patients with chronic pain. Another goal is to improve hand providers’ understanding of the medications their pain colleagues prescribe in shared patients. Pharmaceuticals are an important component in the treatment of chronic pain and opioids are often not a good solution. Knowing what other medications are available can improve the care for these challenging patients.

**REFERENCES**


