Several of the hot topics in geriatrics are pain management, medication reduction/deprescribing, and use of off-label medications. Best-practice use of gabapentinoids — gabapentin (Neurontin) and pregabalin (Lyrica) — comfortably fits into all three categories. Examination of the evidence may help health care practitioners make better decisions when prescribing these medications.

The arguments for using gabapentinoids seem sound, at first glance — these drugs appear to be useful for patients. There has been a strong nationwide push to avoid opioids for pain, so some practitioners consider gabapentinoids to be a common “safe” alternative. (In fact, one of us [D.H.] was told exactly this recently by a consulting psychiatrist colleague.) “Neuropathy” is a very frequent diagnosis in the elderly, and everyone knows — certainly from all the advertising in the media! — that gabapentinoids are the drug of choice. But is this true?

Reviewing the Evidence

In our experience, gabapentinoids are not the wonder drugs they might appear to be. Certainly a geriatrician would use a much lower starting dose and increase with more care than would a practitioner in another specialty. However, we have seen a good number of side effects, such as dulling of the patient’s mental status, and we have not seen particularly good efficacy for either neuropathic pain or chronic generalized pain.

This should not come as a particular surprise after looking at the literature. A study several years ago showed that nearly 7% to 10% of the general population has neuropathic pain, and treatment has resulted in only a minimal reduction on the pain scales (JAMA 2015;314:2172–2181). Head-to-head data regarding which treatment is best are limited. A systematic review and meta-analysis looked at the number needed to treat (NNT) for pain relief with a variety of medications, and found a lower NNT for tricyclic antidepressants than for gabapentinoids (Lancet Neurol 2015;14:162–173).

A much more in-depth review of off-label use of gabapentinoids was published this year by Christopher W. Goodman, MD, and Allan S. Brett, MD, of the University of South Carolina School of Medicine (JAMA Intern Med 2019;179:695–701), and we highly recommend you seek out this article to read for yourself. Its conclusion speaks for itself: “Clinicians who prescribe gabapentinoids off-label for pain should be aware of the limited evidence and should acknowledge to patients that the potential benefits are uncertain for most off-label uses.”

The only pain-related indication that is approved by the U.S. Food and Drug Administration (FDA) for gabapentin is for postherpetic neuralgia. For pregabalin, the pain-related indications are limited to postherpetic neuralgia, neuropathic pain associated with diabetes or spinal cord injury, and fibromyalgia. (An additional indication — not related to pain — is partial-onset seizures as an adjunct therapy for both gabapentin and pregabalin.)

Drs. Goodman and Brett present several interesting facts. They noted that use of gabapentinoids has tripled over the past fifteen years. Gabapentin was the tenth most commonly prescribed medication in the United States in 2017, and pregabalin ranked sixth in nondiscounted spending for brand-name drugs that same year (with that spending rising from $2.4 to $4.9 billion). For the evidence addressing off-label gabapentinoid use, their noteworthy findings included:

1. The evidence is mixed at best for the use of gabapentin for painful diabetic neuropathy.
2. There are few studies of gabapentinoids for nondiabetic neuropathies.
3. The evidence does not support gabapentinoid therapy for low back pain or radiculopathy.
4. Although pregabalin is FDA approved for fibromyalgia, gabapentin is not. However, gabapentin is frequently prescribed for this indication because of its lower cost. In the only placebo-controlled trial, the use of gabapentin resulted in a mean pain difference of only 0.9 on a 0 to 10 scale. As they also point out, this is similar to the mean differences in the trials that resulted in pregabalin’s FDA approval for fibromyalgia. (Take that for what you will.)
5. Both pregabalin and gabapentin are FDA approved for postherpetic neuralgia, defined as pain persisting at least three months after acute herpes zoster. However, there is no evidence to support the efficacy of either drug for acute zoster pain.
6. In the small number of placebo-controlled gabapentinoid trials for various other pain syndromes, with few exceptions the drugs were either ineffective or were associated with small analgesic effects that were statistically significant but of questionable clinical importance.

The evidence cited to support the general use of gabapentinoids in neuropathic pain is often extrapolated inappropriately, according to Drs. Goodman and Brett. “The wording in many guidelines and review articles reinforces an inflated view of gabapentinoid effectiveness or fails to distinguish carefully between evidence-based and non-evidence-based recommendations,” they state. “One unintended effect of the broad definition [of neuropathic pain] might be to create a mistaken perception that an effective drug for one type of neuropathic pain is effective for all neuropathic pain, regardless of underlying etiology or mechanism.”

The 2016 guidelines from the U.S. Centers for Disease Control and Prevention (CDC) on opioid prescribing offer an example of this misapprehension (JAMA 2016;315:1624–1645). The guidelines broadly state that gabapentinoids are a first-line treatment for neuropathic pain — without any further details or specification. Although the two drugs are regarded as interchangeable, published direct comparisons in double-blind studies in patients with chronic noncancer pain are virtually nonexistent.

Clinical Off-Label Prescribing

Drs. Goodman and Brett also include six common clinical scenarios involving problematic off-label gabapentinoid use that are encountered “repeatedly” in both inpatient and outpatient settings. These drugs are undoubtedly seen in the post-acute and long-term care setting. In fact, when one of us [D.H.] was recently visited in the office by a representative of Alosa Health, an academic detailing group, to talk about managing chronic pain in the elderly, gabapentinoids were included.

The group’s evidence-based approach for drug options included pregabalin as “potentially favorable” for osteoarthritis, diabetic neuropathy, and fibromyalgia, and gabapentin only for fibromyalgia (http://bit.ly/2DOEsAR). They noted that the American Diabetes Association (ADA) guidelines recommend pregabalin or duloxetine as an initial treatment for diabetic neuropathy pain, reserving gabapentin for patients who are unable to afford pregabalin (Diabetes Care 2017;40:136–154). Incidentally, Alosa Health’s two “potentially favorable” nondrug interventions for painful diabetic neuropathy are tai chi and transcutaneous electrical nerve stimulation (TENS), and the only “favorable” drug intervention is duloxetine, with nearly half of patients having a 50% reduction in pain in an older study (Pain 2005;116:109–118). One of us [D.H.] has also favorably (and admittedly anecdotally) seen better results and tolerability with duloxetine as compared with the gabapentinoids.

Because gabapentin is FDA approved for the treatment of postherpetic neuralgia in adults and as an adjunct therapy

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for the treatment of partial-onset seizures, the use of this medication for anything other than these indications is considered off-label. One of us [J.M.] called Pfizer to request copies of the off-label studies for gabapentin and pregabalin for the treatment of neurogenic pain before writing this article and received nine pages worth of articles to review!

Dosage Calculation
Kidney function and creatinine clearance (CrCl) must be considered when prescribing gabapentinoid medications. The product labels for gabapentin and pregabalin both recommend the use of the Cockcroft and Gault formula (https://www.kidney.org/professionals/KDOQI/gift_calculatorCock) to calculate CrCl in milliliters per minute.

Gabapentin is currently available as 100, 300, and 400 mg capsules, as well as 600 and 800 mg tablets and a 50 mg/mL oral solution. Pregabalin generic, which was approved in August 2019, is available as 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules and as controlled-release tablets at 82.5, 165, and 330 mg. Additionally, a 20 mg/mL solution is available.

For patients who have normal CrCl, titration to the highest dose of gabapentin — 1,200 mg as two 600 mg tablets, three times a day — adds six pills a day to the patient’s current medication regimen. A swallowing evaluation may need to be completed to ensure there are no issues with the tablet/capsule size. The tablets are scored and can be broken in half to aid in swallowing; unused broken tablets should be disposed of if not used within 28 days. Gabapentinoids must be tapered over at least seven days.

Overall, the pharmacokinetic profiles of gabapentin and pregabalin are somewhat similar, as Drs. Goodman and Brett discuss in their review. However, the two drugs also have some significant differences, so they are not interchangeable (Pharmacy Times, Sept. 22, 2015; http://bit.ly/2BynHz).

Adverse Effects and Misuse
The common adverse reactions to all gabapentinoids include a variety of specific and nonspecific effects including, but not limited to, seizures, suicidal thoughts, somnolence, dry mouth, edema, blurred vision, abnormal thinking, dizziness, peripheral edema, ataxia, and fatigue.

For elderly patients with multiple comorbid conditions who reside in a long-term care facility, these adverse effects may not be recognized or may be mistaken for new conditions — with treatment initiated accordingly, and medications added. Even as this prescribing cascade occurs, the pain symptoms being treated with a gabapentinoid may not be relieved.

Because the United States is in the midst of an epidemic opioid crisis, despite the lack of resources or data to support the use of gabapentinoids for the treatment of neurogenic pain, they are being prescribed as an alternative. Again, gabapentinoids are not the answer except in the case of postherpetic neuralgia.

Thus, an important issue raised by Drs. Goodman and Brett is that the misuse and abuse of gabapentin has become more prevalent in recent years. It is most often abused by multidrug users who combine it with other substances to increase the desired effects, and its misuse has increased along with the worsening of the U.S. opioid crisis.

Use of higher-than-recommended doses of gabapentinoids to achieve euphoric highs is being increasingly reported (Med Lett Drugs Ther 2018;60[1540]). Due to the increasing abuse potential and “high” sensation when opioid users take gabapentinoids, pregabalin is considered a federal Schedule V drug in the United States. Gabapentin is not federally scheduled, and its controlled scheduling differs by state. It is treated as a controlled substance by Kentucky, Michigan, Tennessee, Virginia, and West Virginia (Carcisde Medical, June 10, 2019; http://bit.ly/35TQ9ms).

Gabapentinoids or Not?
The results of placebo-controlled studies for the gabapentinoids do not provide compelling evidence that they are effective for the treatment of pain, yet payors have been seeing an increase in gabapentin and pregabalin oral use. More recently these drugs are being used as topical compounds, even though there are no gabapentinoid formulations currently approved for topical use.

We believe this information will be helpful to you in your practice. It is certainly something you can use in your role as an educator to colleagues and staff. And, importantly, make sure all of your patients get the shingles vaccine — if you never get shingles, you will never have postherpetic neuralgia!

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