Panel discussions

HAROLD H. MORRIS III, MD, EDWARD C. COVINGTON, MD, GARY S. SACHS, MD, AND JONATHAN R.T. DAVIDSON, MD

Question: Gabapentin comes across as quite a safe drug. Are there any administration guidelines that need to be considered when prescribing this agent?

Dr. Morris: Gabapentin is a safe compound, but there are some precautions that must be observed. Gabapentin is a renally excreted drug, and any drug that must be cleared depends on the adequate maintenance of physiologic systems. As one ages, renal clearance decreases, and as a result levels of gabapentin may rise. For practical purposes, however, as long as BUN and creatinine levels remain normal, it will not be necessary to alter gabapentin dosages.

Question: Can you elaborate on the cognitive effects of topiramate therapy?

Dr. Morris: The cognitive toxicity of topiramate is highly idiosyncratic: there is no way to predict which patients will be affected by it. When it does occur, it may become evident with doses as low as 50 to 100 mg. But some people are extremely tolerant, and can safely receive up to 1800 mg/day of topiramate without any problem. Cognitive toxicity may also be insidious; patients themselves may not recognize its onset, and family and friends may recognize the symptoms first. The cognitive side effects respond to dose reductions, potentially even disappearing if the dose is reduced sufficiently.

Question: I have heard of a similar syndrome of insidious dementia occurring with valproate. Is this a documented effect?

Dr. Morris: Yes, but rather than a simple dementia, the true profile of this adverse reaction includes a parkinsonian syndrome, as well as a loss in cognition and slowed thinking. This picture also is reversible on discontinuation of therapy.

Question: Are there any guidelines for determining which anticonvulsant is best to use for different sources of pain?

Dr. Covington: At this point, I consider gabapentin the first-choice agent for pain of most origins. It has few drug-drug interactions because it does not metabolize and does not undergo autoinduction, and, because of its simple transport and excretion, it is not necessary to monitor liver and hematologic indices. One of its most important advantages is its wide spectrum of activity. Gabapentin is a very safe agent, with few side effects, making it a logical choice for the empiric treatment of idiopathic pain.

Question: Is clonazepam the only benzodiazepine effective in the treatment of neuropathic pain?

Dr. Covington: Yes, although the reasons for this unique activity are unknown. Pain relief has not been observed with any of the other benzodiazepines, including diazepam, lorazepam, or alprazolam.

The main drawback of clonazepam in the treatment of neuropathic pain is its risk for dependence. I prefer to use a drug with no addiction potential whenever I can, rather than chance substance abuse. Therefore, I usually reserve clonazepam therapy for recalcitrant pain states.

Question: In my experience, gabapentin ameliorates the restless leg syndrome at doses as low as 100 mg per night. Is it also effective for pain relief at unexpectedly low doses?

Dr. Covington: Many pain patients respond to treatment with 900 mg/day gabapentin, which is a relatively low dose. Some patients, however, taking 300 mg tid gabapentin will regress between doses, experiencing renewal of pain before the next dose is scheduled. Yet in drug-naive patients, especially the elderly, it is important to begin treatment at a low dose and titrate up cautiously. During this titration

period, the initial response that occurs shortly after drug intake may wear off before it is time to take the next dose. It is important that the physician, as well as the patient, be aware of this potential lag and know that it will resolve with further drug titration.

Question: What is the protocol for managing benzodiazepine withdrawal with anticonvulsant drug therapy?

Dr. Covington: Benzodiazepine withdrawal therapy is not a science and must be individualized. Although there are equivalency tables meant to enable slow conversion away from benzodiazepine by adding increasing doses (to equal effect) of the therapeutic anticonvulsant, there are several problems with this approach. First, many patients are not aware of exactly what dose of benzodiazepine they have been ingesting, and so it is impossible to equivalently convert. Second, some patients forget how much drug they have ingested. Lastly, some patients simply are not truthful about how much they have been taking.

Therefore, I find it most expeditious to simply discontinue the benzodiazepine immediately and prescribe in its place 600 mg of gabapentin. The gabapentin dose is then repeated every 4 (to 6) hours, even dosing in the middle of the night if necessary in the early stages of transition. Within a week, I try to reduce the dosing period to q6h, then to 400 mg q6h, with continuing reductions until discontinuation is possible. All along I follow the patient with tendon taps, pulse measurements, and other objective evaluations.

It is difficult to predict an optimal anticonvulsant dose or the duration of withdrawal therapy. No reliable response prediction parameters have been recognized. Instead, the anticonvulsant dose is titrated upward and back downward based on autonomic signs and hyperreflexic responses indicative of a withdrawal reaction.

Question: Do the different benzodiazepines yield unique response and withdrawal patterns to gabapentin use?

Dr. Covington: No. Withdrawal from any of the benzodiazepines appears to follow a similar pattern, and all respond to gabapentin therapy.

Question: Dr. Sachs, your lamotrigine vs. placebo slide (*Figure 4, page SI-35*) shows a placebo response rate of 25% to 30%. In epilepsy, placebo rates are around 8% to 10%, and if they are higher, we worry about the validity of the study. Can you comment on this?

Dr. Sachs: Placebo response rates in bipolar depression studies are just over 25%. The rate in the study I showed is actually much lower than in almost any other study you are going to see in psychiatry.

Typically, placebo rates have been around 30%. In anxiety disorder studies, it is hard to show a benefit for any drug, not because the drugs are not working, but because the placebo responses are very high. So, 25% is not out of line for psychiatry.

Question: My question is related to your inpatient treatment of acute mania with gabapentin. Why are you using such low doses of gabapentin when you have someone completely controlled in the hospital? Why don't you give them 3600 mg on day one?

Dr. Sachs: I think it is mainly because we don't know that we can do that. We know that we can do that with divalproex, but we do not know what will happen with gabapentin.

There are patients who respond beautifully to 300 mg/day. They sleep; they are sedated the next day. You wish you knew who was going to have which type of response. But we are doing this over a period of days.

If somebody would do a study and let us know that we could start at 3600 mg or that starting at 300 mg and stepping up is just as useful, then we would be able to do it. But right now we do not have the data.

Question: Why doesn't psychiatry come up with mood stabilizers that are not anticonvulsants, that are not antihypertensives, like calcium channel blockers? The medications we use are clearly potent, and yet we are beginning to treat more and more bipolar patients with them, especially children. Why are we not looking for membrane stabilizers that do not have some of these more toxic side effects?

Dr. Sachs: Omega-3 fatty acids may be an example of that. But often, we are reinventing the wheel for the most part. Once we see what seems to work, we do variations of it until we have another serendipitous finding.

It is very hard to know what is likely to work. As we are beginning to get classes of drugs that actually can target specific mechanisms, such as the phosphoinositol cycle, it becomes really interesting. There are new classes of drugs on the way; they are just not yet studied. So, we are looking; we just do not have them yet.

Question: I understand your rationale as far as lamotrigine, but given the neurologists' experience with this, why not step up the rate?

Dr. Sachs: In Germany they have started at 200 mg and their rash rate is 40%. To me, that is a good reason not to go faster. We start at 25. Rash usually happens within 6 to 8 weeks, and you do have to worry about it later. There are serious late-occurring rashes; it is just that they are less common. Most of them have occurred in the 6- to 8-week range.

Question: Dr. Davidson, in your trial, patients received gabapentin for 14 weeks. Is this the anticipated duration of therapy in a nontrial setting?

Dr. Davidson: No, in clinical management 14 weeks is an inadequate treatment period for social phobia. It is more likely that gabapentin treatment will continue for at least 12 months. Earlier discontinuation is associated with a high likelihood of relapse.

In these trials relapse rates ranged from a low of 20% to a maximum rate of about 100%. The latter figure resulted from discontinuation of maclobamide, clonazepam termination led to relapse in 20%, brofaromine in about 70%, and paroxetine in approximately 60% of patients after 6 to 12 months of treatment.

Question: In using gabapentin, I have observed excellent compliance among patients, not simply because it is an easy medicine to take, but also because it improves the patient's sense of well-being as well as his or her cognitive function, especially the sense of objectivity. People begin to sound more mature and self-assured. Are these established features of gabapentin therapy?

Dr. Davidson: Yes, patients receiving gabapentin experience not only improvement in clinical symptoms but also greater insight and mature thinking. One of the reasons gabapentin has been so well-received as treatment of social phobia is for exactly that reason. Gabapentin has a disinhibiting effect. Social phobia, being a distinct pathologic inhibition and fear of expressing opinions, benefits greatly from this particular feature of gabapentin.