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Gabapentin: A new addition to the armamentarium for alcohol dependence?

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Anticonvulsants, a diverse class of medications, reduce neuronal excitability and prevent seizures, acting at a range of different molecular targets, including sodium channels, and the glutamate and γ -aminobutyric acid (GABA) systems. Beyond the prophylaxis of seizures, anticonvulsants have proven useful in a number of other disorders, including various chronic pain syndromes and bipolar and other mood disorders. There has been long-standing interest in anticonvulsants for the treatment of alcohol dependence. Studies of anticonvulsants, most commonly carbamazepine, for treatment of acute alcohol withdrawal began to emerge in the 1970s, based in part on the typical occurrence of seizures, as well as autonomic hyperactivity, during alcohol withdrawal. Anticonvulsants lack abuse potential, which is a desirable feature for treating alcohol dependence. The consensus is that anticonvulsants are useful adjuncts in the treatment of alcohol withdrawal but do not fully substitute for benzodiazepines, which remain the treatment of choice (1).

The hypothesis that anticonvulsants might be beneficial in the chronic treatment of alcohol dependence, to induce and maintain abstinence and prevent relapse, stems in part from the notion of subacute alcohol withdrawal—that the syndrome of alcohol withdrawal has a long tail with symptoms like sleep disturbance, anxiety or stress sensitivity persisting for weeks after completion of acute detoxification. Two large, placebo-controlled trials have now supported the efficacy of the anticonvulsant topiramate for the treatment of alcohol dependence (2,3). Topiramate also reduces appetite, helping with weight loss, and has shown some promise for treatment of cocaine dependence. Topiramate has a complicated mechanism of action. Its impact on addictive and appetitive behaviors has been hypothesized to relate in part to its glutamatergic and GABAergic effects modulating the brain reward system (4). A drawback of topiramate is its adverse effect profile, which may include cognitive impairment, sedation, and renal acidosis and kidney stones resulting from carbonic anhydrase inhibition.

In this context, the demonstration of the efficacy of gabapentin for relapse prevention among alcohol-dependent patients by Mason et al. (5) in this issue is an important development. This well-designed and well-powered trial replicates the positive findings of several

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previous smaller trials. Gabapentin potentiates GABA activity indirectly, perhaps partly through its interaction with voltage-sensitive calcium channels. Gabapentin is a well tolerated medication, with few adverse effects at low to moderate doses, although typical anticonvulsant adverse effects (e.g., sedation, dizziness) may occur at higher doses. It does not seem to have abuse potential. It is already widely prescribed for treatment of chronic pain, mood, anxiety, and sleep problems, in addition to seizure prophylaxis. It would thus seem to have potential for widespread use for treatment of alcohol dependence in both specialty and primary care treatment settings.

An important point is that the present trial took place among outpatient alcoholics, who were able to abstain from alcohol for several days prior to initiating gabapentin. In future research, it would be useful to determine whether the efficacy of gabapentin depends on an initial period of abstinence, and what this says about its mechanism. With naltrexone, the opioid receptor antagonist approved by the US Food and Drug Administration (FDA) for treatment of alcohol dependence, there is also evidence that the beneficial effect occurs mainly among patients able to abstain briefly at the outset of treatment (6). Does this mean these medications are effective among the more mild to moderately ill alcoholics who can stop drinking for a few days at a time? Or, would the medications be equally effective among more severe alcoholics who undergo a medically supervised detoxification prior to starting the medication? In any case, a large proportion of alcohol-dependent patients presenting in primary care settings fall in the mild to moderate range of severity. This, again, suggests the strong potential for gabapentin in the treatment of alcohol dependence in primary care.

A larger issue is that we now have three FDA-approved medications for the prevention of relapse in alcohol dependence -- disulfiram, naltrexone hydrochloride, and acamprosate calcium -- as well as topiramate, and now gabapentin -- that have a substantial evidence base. Yet, medications for alcohol dependence are sorely underutilized. Approval by the FDA would be one helpful step. This raises the question of whether there are plans to seek FDA approval of gabapentin for alcohol dependence, whether the FDA would require further trials to confirm efficacy and safety, and who would serve as the sponsor. Since gabapentin is off-patent, there is limited financial incentive for a pharmaceutical firm to assume sponsorship, and government support would probably be needed to make this happen.

While most alcohol-dependent patients present in primary medical care settings, the societal burden of alcohol dependence and other addictions remains enormous. Psychosocial treatments, including Alcoholics Anonymous and various counseling methods, have been the traditional mainstay of treatment for alcohol dependence. However, these are not effective in all cases. Nor are the medications. In the trial reported in this issue, the number needed to treat (NTT) for gabapentin on the key outcome of abstinence from heavy drinking is 5. Similar NTT estimates apply to naltrexone for alcohol dependence (7), and, for that matter, for the treatment of depression with any given antidepressant medication. This means that, on average, 5 patients need to be treated to see 1 true medication responder. But, the treatments act by different mechanisms, and if 1 fails another may work. The key is to keep trying different approaches, or combinations. We are arguably now in a position with

respect to alcohol dependence similar to our position for other chronic conditions like depression or hypertension, with a number of different treatment options, both psychosocial and pharmacological. Getting medications more routinely utilized will require getting physicians more involved in the treatment of alcohol dependence. This means 1) more training, in medical school through residency and continuing medical education; 2) more support for specialty training in the addictions, currently offered through the addiction psychiatry subspecialty of the American Board of Psychiatry and Neurology, and the addiction medicine specialty supported by the American Board of Addiction Medicine; and 3) an embrace by all physicians, particularly those in primary care specialties, of the mandate to recognize and treat alcoholism and other addictions.

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