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▶ An open trial of gabapentin in acute alcohol withdrawal using an oral loading protocol.

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Alcohol and Alcoholism: 2010, 45(2), p. 143–145.

Drawbacks of the favoured benzodiazepine drugs used to ameliorate alcohol withdrawal have led to trials of anticonvulsants, but this German trial found one promising anticonvulsant effective only among less severe cases, and even then some seemingly doing well later developed epileptic seizures, one of the most severe consequences of alcohol withdrawal.

Summary Benzodiazepines (and in some European countries, clomethiazole) are the pharmacological treatments of choice in the management of the alcohol withdrawal syndrome. To avoid their propensity for dependence and other drawbacks of these drugs, novel anticonvulsants have been studied, of which gabapentin seems promising both due to its pharmacological profile and some animal studies and reports involving human subjects. But the only published placebo-controlled human clinical trial did not find gabapentin superior to placebo as an adjunct to clomethiazole. In that trial moderate gabapentin initial doses around 400mg (increased to 1600mg in the first 24 hours) did not ameliorate the severity of withdrawal.

Given this finding, the featured study instead tried a higher initial gabapentin dose of 800mg, which can be expected to show effects within two to three hours. The study involved 10 women and 27 men admitted to a German hospital for treatment of severe alcohol withdrawal, defined as scoring at least 15 points on the Clinical Index of Alcohol Withdrawal-Revised scale, a standard way of assessing withdrawal severity. They were selected to be free of other substance use disorders (except smoking) and not using certain medications.

Patients who within two hours responded well to the initial 800mg of gabapentin (the 'early responders'), identified by withdrawal severity remitting to under 15 points, were given further doses totalling 3200mg in the first 24 hours. Further doses were given on the following days until on day four the dose started to be reduced.

Patients who after two hours had not responded well to the initial 800mg were switched to the unit's usual regimen based on clomethiazole or clonazepam.

Main findings

Of the 37 patients, 27 were classified as early responders. In the first two hours their withdrawal severity fell from on average 17 points to eight. However, over the next 36 hours two experienced seizures and another worsening withdrawal symptoms and were switched to clonazepam, meaning that only 24 completed the study as 'responders'. The early responders averaged nearly 11 days' inpatient treatment.

The other 10 patients averaged at the start 20 points on the withdrawal severity scale, which despite the initial gabapentin dose deteriorated to nearly 22 points within two hours. The two patients with initially the most severe withdrawal symptoms were both among them. They averaged about a fortnight in hospital. They differed from the responders by: having initially more severe withdrawal symptoms, probably accounting for their longer treatment; and by significantly more severe initial symptoms of anxiety and depression. Their heart rates and blood pressures also tended to be higher and they smoked more cigarettes. However, they did not significantly differ from the early responders in terms of their drinking histories, number of alcohol-associated consequences, laboratory results and ECG changes.

With the exception of the two seizures, no other serious adverse events were recorded.

The authors' conclusions

In this study patients who did not respond to gabapentin were characterised by more severe withdrawal symptoms exceeding 20 points and more severe symptoms of anxiety and depression. It seems therefore that the evaluated gabapentin regimen is helpful only for less severe and less complicated acute alcohol withdrawal. Similar conclusions have drawn from other trials. However, its utility even among these patients is compromised by the fact that two who at first seemed to be doing well on gabapentin later developed epileptic seizures.

FINDINGS The two seizures are a major concern, because benzodiazepines became the mainstay of alcohol withdrawal treatment to avoid these and other serious consequences. These drugs made seizures largely avoidable, and any change in treatment which resurrects this threat to patient welfare is on those grounds a step backwards. The featured study's authors speculate that in this study they happened but not in a previous study, because the waiting period before further medication was two hours rather than one. It could also be that this was a chance finding somewhat out of line with other alcohol withdrawal studies, on which more below.

As well as benzodiazepines, British guidelines recommend considering not gabapentin but another anticonvulsant, carbamazepine, and also chlormethiazole (Heminevrin), a drug with anticonvulsant and sedating properties. The experts did so after reviewing studies

across which there were no significant differences between these agents in the incidence of alcohol withdrawal seizures and other adverse effects, or in their abilities to ameliorate withdrawal symptoms. The guidelines also recognise the reasons why attention has turned to gabapentin and other alternatives to benzodiazepines – that the latter have attractions for people dependent on alcohol due to their tranquillising and sedating properties which risk abuse and dependence.

A review conducted for the Cochrane collaboration which evaluated the effectiveness and safety of anticonvulsants in the treatment of alcohol withdrawal found them not significantly better than placebos, though possibly better at preventing seizures, and no better than alternative medications, except perhaps in respect of ameliorating withdrawal symptoms.

Another Cochrane review focused on benzodiazepines for alcohol withdrawal found these drugs definitely prevent seizures compared to a placebo, and compared to other drugs tended non-significantly to be better at preventing or controlling seizures and delirium, severe life threatening side-effects, treatment drop-out, and drop-out due to side effects. In relation specifically to anticonvulsants, there were no significant differences, but benzodiazepines tended to result in greater improvements in the doctor's global assessment of the patient's wellbeing, but also an increased risk of alcohol withdrawal seizures. The latter possibility rested on two trials, one of which compared carbamazepine against oxazepam and the other chlormethiazole against alprazolam. Each recorded no seizures among the anticonvulsant patients but one among the respectively 29 and 46 patients administered benzodiazepines.

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