CHAPTER 29

Alcohol-related seizures

G. Bråthen,1 E. Ben-Menachem,2 E. Brodtkorb,1 R. Galvin,3 J. C. Garcia-Monco,4 P. Halasz,5 M. Hillbom,6 M. A. Leone,7 A. B. Young8

1Trondheim University Hospital, and Norwegian University of Science and Technology, Trondheim, Norway; 2Institute of Clinical Neuroscience, SU/Sahlgrenska Hospital, Gothenburg, Sweden; 3Cork University Hospital, Wilton, Cork, Ireland; 4Hospital de Galdacano, Galdacano (Vizcaya), Spain; 5National Institute of Psychiatry and Neurology, Epilepsy Center, Budapest, Hungary; 6Oulu University Hospital, Oulu, Finland; 7Ospedale Maggiore della Carità, Novara, Italy; 8Dunsyre House, Dunsyre Carnwath, Lanark, UK

Background

It has been known since Hippocratic times that alcohol overuse causes epileptic seizures [1]. The nature of this relationship is complex and poorly understood. Despite being a considerable problem in neurological practice and responsible for one-third of seizure-related admissions [2–5], there is little consensus as to the optimal investigation and management of alcohol-related seizures. Furthermore, different treatment traditions and policies exist, and vary from country to country [6]. These guidelines summarize the current evidence for the diagnosis and management of alcohol-related seizures.

Methods

The task force systematically searched MEDLINE, EMBASE, the Cochrane databases, and several other sources for relevant trials related to a set of pre-defined key questions. Recent papers of high relevance were reviewed. Consensus was reached by discussions during meetings of the task force at EFNS congresses and at a workshop. The guideline was originally published in 2005 [7]. The literature search for the present update was performed in October 2009. The evidence (Class I–IV) and recommendation levels (A–C) were applied in accordance with Brainin et al. [8]. Some important aspects of patient management that lack the evidence required for recommendations have been included; these are marked GPP, for ‘Good Practice Points’.

Results

Diagnosis of alcohol-related seizures

History taking

Unless alcohol withdrawal symptoms are unequivocally present, the clinical diagnosis of an alcohol-related seizure can only be made by obtaining a drinking history that indicates alcohol overuse prior to the seizure. As patients frequently underreport true levels of alcohol consumption, there is a need to control for this bias. Therefore, whenever possible, a relative or friend should be asked about the recent alcohol intake.

Several other legal or illegal pharmacological agents may influence the tendency to have seizures, due either to withdrawal (e.g. benzodiazepines) or to a direct neurotoxic effect (e.g. antipsychotics, antidepressants, or stimulant drugs). These factors may complicate the clinical picture and should be considered in the diagnosis of alcohol-related seizures.

A good drinking history includes both the quantity and frequency of alcohol intake and changes in drinking pattern, at least during the previous 5 days, as well as the time of the last alcohol intake (GPP).
Structured questionnaires have been developed to reveal and grade excessive alcohol consumption as well as alcohol overuse and dependence. To be clinically useful a questionnaire needs to be both brief and reliable. The probably most commonly applied instrument is CAGE, which is the acronym for a simple four-question item. It is brief, easily memorized, and has reasonably fair accuracy [9]. However, it fails to detect binge drinking, which is probably best assessed by directly asking for the largest number of drinks in a single drinking occasion [10]. The Alcohol Use Disorders Identification Test (AUDIT) includes this item. It is a 10-item questionnaire which requires a 2–3 min interview and provides a fine-pitched grading (0–40) of alcohol use and overuse. For patient populations with lower drinking levels, it has higher accuracy than other questionnaires [11, 12] but is not easily memorized and may be perceived as too long for routine use in busy medical settings. A handful of brief versions, e.g. AUDIT-C, FAST, and AUDIT-PC, consisting of 3–5 AUDIT items, or Five-SHOT, a combination of AUDIT and CAGE items, have all shown good accuracy compared to AUDIT [13–16]. Other questionnaires, such as the Brief Michigan Alcoholism Screening Test (Brief MAST) [12] and the Munich Alcoholism Test (MALT) [17] have widespread use, but do not offer better accuracy than AUDIT or its brief versions, and their use in a routine clinical setting is more demanding.

**Recommendation**

Questionnaires offer high diagnostic accuracy for alcohol overuse (Level A recommendation). To identify patients with alcohol-related seizures and binge drinking, brief versions of AUDIT are recommended as they are accurate and easy to use in busy clinical settings (Level A recommendation).

Carbohydrate-deficient transferrin (CDT) and gamma-glutamyl transferase (GGT) are sensitive markers for alcohol overuse, although GGT is less specific than CDT. Systematic literature reviews have been inconclusive as to which marker is better [22, 23]. Both CDT and GGT show poor accuracy as screening instruments for alcohol-related seizures in unselected seizure populations [20]. Attempts to combine the tests have led to increased sensitivity [24–26]. As the current intoxication level is important information with potential treatment consequences [27], blood alcohol should be measured in patients with suspected alcohol-related seizures (GPP).

**Recommendation**

CDT and GGT have a potential to support a clinical suspicion of alcohol overuse when the drinking history is inconclusive (Level A recommendation). Due to poor accuracy in unselected populations, biomarkers should not be applied as general screening instruments (Level C recommendation).

**Patient examination and observation**

The clinical examination should be focused on features distinctive of either epilepsy or withdrawal seizures (table 29.1). To predict the severity of alcohol withdrawal, the revised Clinical Institute Withdrawal Assessment Scale (CIWA-Ar) can be applied [30]. The CIWA-Ar takes 2–5 min to administer and grades withdrawal severity on a scale from 0 to 67 (available as appendix to this guideline on www.efns.org). More than 90% of alcohol withdrawal seizures occur within 48 h of cessation of a prolonged drinking bout [4, 31]. Patients should be observed in hospital for at least 24 h, after which a clinical risk assessment should be made with respect to development of symptoms of alcohol withdrawal (GPP).

For the general treatment of the alcohol withdrawal syndrome readers should refer to guidelines [32, 33, 34, 35].

**Recommendation**

The CIWA questionnaire can be applied to grade the severity of withdrawal symptoms and give support to the decision on whether to keep or discharge the patient (Level A recommendation).
Electroencephalography (EEG)
The incidence of EEG abnormalities (slow or epileptiform activity) is lower among patients with alcohol withdrawal seizures (AWS) than in those with seizures of other aetiology. Therefore, EEG pathology suggests that the seizure may not have been caused exclusively by alcohol withdrawal [31, 39].

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<td>EEG should be recorded after a first seizure. Subsequent to repeated AWS, EEG is considered necessary only if an alternative aetiology is suspected (Level C recommendation).</td>
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Patient management
Subsequent to the acute treatment of alcohol-related seizures, attention should be given to other potential complications of alcohol overuse such as thiamine deficiency, electrolyte disturbances, acute intracranial lesions, infections, and development of the alcohol withdrawal syndrome, potentially leading to delirium tremens. Apart from acute intracranial lesions, which fall outside the scope of these guidelines, these factors are addressed below.

Thiamine therapy
Prolonged heavy drinking causes reduced absorption and increased excretion of thiamine. Only 5–14% of patients with Wernicke’s encephalopathy are diagnosed in life [40, 41]. The majority (~80%) of those who show CNS lesions caused by thiamine deficiency are chronic alcohol overusers [40, 42]. Thiamine is a comparatively harmless vitamin, the diagnosis of thiamine deficiency is difficult, and the consequences of not treating may be severe. Therefore, the threshold for starting therapy should be low. Oral administration is insufficient as the intestinal thiamine absorption may be severely impaired [43]. In a recent Cochrane review, only one sufficiently large randomized double-blind trial on the preventive effects of different doses of thiamine could be identified [44], from which it could only be concluded that a daily dose of 200 mg thiamine was better than 5 mg [45]. For the treatment of imminent or manifest Wernicke’s encephalopathy, uncontrolled trials and empirical clinical practice suggest a
daily dose of at least 200 mg thiamine parenterally for minimum 3–5 days. In our experience, patients with Wernicke’s encephalopathy may benefit from continued treatment for more than 2 weeks (GPP).

**Recommendation**
Before starting any carbohydrate-containing fluids or food, patients presenting with known or suspected alcohol overuse should be given prophylactic thiamine in the emergency room (Level B recommendation).

**Treatment of electrolyte disturbances**
Due to large fluid intake (beer), hyponatraemia may develop in alcohol overusers. The serious disorder of central pontine myelinolysis is thought to be triggered by osmotic gradients in the brain, a situation that may well result from attempts to correct this electrolyte disturbance rapidly [46]. Hyponatraemia in alcohol overusers generally shows a benign clinical course [47], and usually repairs with cessation of alcohol intake and re-institution of a normal diet [48]. If infusion is considered necessary, according to a retrospective study the rate of serum sodium correction should not exceed 10 mmol/day [49]. The evidence is insufficient for treatment recommendations.

Hypomagnesaemia and respiratory alkalosis seem to be associated with alcohol withdrawal, and correction of hypomagnesaemia may raise the seizure threshold in the initial phase of alcohol withdrawal [50]. Unresponsiveness to parenteral thiamine therapy is a possible consequence of hypomagnesaemia [51]. However, there is not sufficient evidence to recommend routine correction of hypomagnesaemia.

**Drug options for primary prevention of alcohol withdrawal seizures**
An ideal drug for symptom relief during detoxification from alcohol should display fast loading, long duration, minor side effects, low toxicity, few interactions, minimal overuse potential, and high efficacy in preventing both withdrawal symptoms in general as well as seizures. Drugs should be available in more than one form, liquid being particularly useful for some patients. Apart from overuse potential, benzodiazepines (BZD) fulfil all the above listed criteria for an ideal drug. BZD are cheap, widely available, and have a well-documented safety profile.

In meta-analyses of controlled trials for primary prevention of AWS, a highly significant risk reduction for seizures with BZD compared with placebo have been demonstrated [53, 56]. Drugs with rapid onset of action (diazepam, lorazepam, alprazolam) seem to have higher overuse potential than those with slower onset of action (chlordiazepoxide, oxazepam, halazepam). For the purpose of reducing the risk of seizures due to BZD withdrawal and reducing rebound withdrawal symptoms after discontinuation, long-acting drugs should be preferred to short-acting ones [33, 53]. However, short-acting BZDs may have advantages for patients with respiratory insufficiency. Symptom-triggered treatment has been reported to be as effective as fixed-dose or
loading therapy, resulting in lower doses and shorter treatment time [57, 58]. Lorazepam has some advantages over diazepam. Despite a shorter half-life it has longer duration of action because it is less accumulated in lipid stores. However, its onset of action is slightly slower than that of diazepam.

In a Cochrane review, the efficacy of anticonvulsants to prevent seizures did not reach statistical significance compared either to placebo, benzodiazepines or other drugs [59].

Many other drugs and drug combinations are being used, including clormethiazole, gamma-hydroxybutyrate, and clonidine, all for which the documentation is insufficient [53, 57, 60, 61].

**Recommendation**

When pharmacological treatment is necessary, benzodiazepines should be chosen for the primary prevention of seizures in a person with alcohol withdrawal, as well as for treatment of the alcohol withdrawal syndrome. The drugs of choice are lorazepam and diazepam. Although lorazepam has some pharmacological advantages to diazepam, the differences are minor and, as i.v. lorazepam is largely unavailable in Europe, diazepam is recommended. Other drugs for detoxification should only be considered as add-ons (Level A recommendation).

**Secondary prevention of withdrawal seizures**

Following a withdrawal seizure, the recurrence risk within the same withdrawal episode is 13–24% [53]. Consequently, there is a good rationale for treating these patients as soon as possible in order to prevent subsequent seizures. Lorazepam reduces recurrence risk significantly [62]. Phenytoin did not prevent relapses in patients who had one or more seizures during the same withdrawal episode [53].

**Recommendation**

Benzodiazepines should be used for the secondary prevention of AWS (Level A recommendation). Phenytoin is not recommended for prevention of AWS recurrence (Level A recommendation). The efficacy of other antiepileptics for secondary prevention of AWS is undocumented.

**Alcohol-related status epilepticus**

Alcohol withdrawal is one of the commonest causes of status epilepticus (SE), and SE may be the first manifestation of alcohol-related seizures. Although SE has probably a better prognosis when alcohol related [63], it increases the risk for subsequent epilepsy [64]. One recent study indicates that lorazepam may be superior to diazepam for the treatment of out-of-hospital SE [65]. In another study comparing four treatments, lorazepam was considered easier to use but not more efficacious than diazepam, phenobarbital, or phenytoin [66].

**Recommendation**

For the initial treatment of alcohol-related status epilepticus, i.v. lorazepam is safe and efficacious. When unavailable, i.v. diazepam is a good alternative (Level A recommendation).

**Management of epilepsy in patients with current alcohol overuse**

The comprehensive management of these patients includes careful counselling and information about the seizure-precipitating effect of alcohol, particularly the concurrent withdrawal of alcohol and antiepileptic drugs (AEDs). Prescription of AEDs to alcohol overusers is often a fruitless undertaking, which may increase their seizure problems due to poor compliance, drug overuse, and drug-alcohol interactions [38]. The ideal drug for such patients should be well tolerated in combination with alcohol and have a benign side effect profile, including safety in overdose [67], and have a suppressive effect on drinking behaviour. In a few small studies, carbamazepine, valproic acid, gabapentin, and pregabalin have each been reported to reduce alcohol consumption [68–71], and topiramate has recently been shown to reduce craving for alcohol [72]. Prophylactic AED treatment should only be considered after recurrent epileptic seizures clearly unrelated to alcohol intake, following the usual guidelines for AED treatment. The available data do not allow for recommendations on this topic.

**How much alcohol can a patient with epilepsy safely consume?**

In various European countries, different advice has been given as to whether patients with epilepsy should abstain
totally from alcohol [73]. Only one randomized controlled clinical study [74] has addressed this particular issue; an intake of one to three drinks each containing 9.8 g ethanol (standard alcohol units; see [75]) up to three times a week did not increase seizure susceptibility in treated patients with partial epilepsy. Another study suggested a seizure risk proportional to the alcohol intake level [76].

Alcohol sensitivity may vary between epilepsy syndromes. Generalized epilepsies, in particular juvenile myoclonic epilepsy, seem to be more sensitive to alcohol, sleep deprivation, and in particular the combination of these factors [77].

**Recommendation**

For the majority of patients with partial epilepsy and controlled seizures, and in the absence of any history of alcohol overuse, an intake of one to three standard alcohol units, one to three times a week, is safe (Level B recommendation).

**Conflicts of interest**

The present guidelines were developed without external financial support. None of the authors report conflicting interests.

**References**

the upper digestive tract. Alcohol Clin Exp Res 2002; 


