

EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force

The EFNS Task Force on Diagnosis and Treatment of Alcohol-Related Seizures
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Despite being a considerable problem in neurological practice and responsible for one-third of seizure-related admissions, there is little consensus as to the optimal investigation and management of alcohol-related seizures. The final literature search was undertaken in September 2004. Consensus recommendations are given graded according to the EFNS guidance regulations. To support the history taking, use of a structured questionnaire is recommended. When the drinking history is inconclusive, elevated values of carbohydrate-deficient transferrin and/or gammaglutamyl transferase can support a clinical suspicion. A first epileptic seizure should prompt neuroimaging (CT or MRI). Before starting any carbohydrate containing fluids or food, patients presenting with suspected alcohol overuse should be given prophylactic thiamine parenterally. After an alcohol withdrawal seizure (AWS), the patient should be observed in hospital for at least 24 h and the severity of withdrawal symptoms needs to be followed. For patients with no history of withdrawal seizures and mild to moderate withdrawal symptoms, routine seizure preventive treatment is not necessary. Generally, benzodiazepines are efficacious and safe for primary and secondary seizure prevention; diazepam or, if available, lorazepam, is recommended. The efficacy of other drugs is insufficiently documented. Concerning long-term recommendations for non-alcohol dependant patients with partial epilepsy and controlled seizures, small amounts of alcohol may be safe. Alcohol-related seizures require particular attention both in the diagnostic work-up and treatment. Benzodiazepines should be chosen for the treatment and prevention of recurrent AWS.

Background

It has been known since Hippocratic times that alcohol overuse causes epileptic seizures (Lloyd, 1978). 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 (Earnest and Yarnell, 1976; Hillbom, 1980; Bråthen *et al.*, 1999; Jallon *et al.*, 1999), 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. 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. The final search was done in September, 2004. Recent papers of high relevance were reviewed. Consensus was reached by discussions during meetings of the Task Force at EFNS congresses and at a separate workshop. The evidence and recommendation levels are graded according to the current guidance (Brainin *et al.*, 2004). Some important aspects of patient management that lack the evidence required for recommendations have been included; these are marked GPP, for 'Good Practice

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Points'. Details of the literature search, method for reaching consensus and additional information on the development of this guideline is available on the Task Force homepage on the European Federation of Neurological Societies (EFNS) website (<http://www.efns.org>).

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, either because of withdrawal (e.g. benzodiazepines) or because of 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).

Questionnaires

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. Probably the most commonly applied instrument is CAGE, which is the acronym for a simple four question item, (available on <http://www.efns.org>). It is brief, easily memorized and has reasonably fair accuracy (Mayfield *et al.*, 1974). 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 (Matano *et al.*, 2003). 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 (MacKenzie *et al.*, 1996; Fiellin *et al.*, 2000) 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 three to five AUDIT items, or Five-SHOT, a combination of AUDIT and CAGE items, have all shown good accuracy compared with AUDIT (Piccinelli *et al.*, 1997; Bush *et al.*, 1998; Seppä *et al.*, 1998; Hodgson *et al.*, 2003). Other questionnaires, such as the Brief Michigan Alcoholism Screening Test (Brief MAST; MacKenzie *et al.*, 1996), and the Munich Alcoholism Test (MALT; Feuerlein *et al.*, 1977) 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).

Biomarkers

For detection of alcohol overuse, questionnaire-based interviews are reported to be more sensitive than any biomarker (Bernadt *et al.*, 1982; Aertgeerts *et al.*, 2002). However, in cases where information on recent alcohol consumption is unavailable or considered unreliable, markers of alcohol consumption can increase the accuracy of the clinical diagnosis (Bråthen *et al.*, 2000; Martin *et al.*, 2002).

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 (Salaspuro, 1999; Scouller *et al.*, 2000). Both CDT and GGT show poor accuracy as screening instruments for alcohol-related seizures in unselected seizure populations (Bråthen *et al.*, 2000). Attempts to combine the tests have led to slightly increased sensitivity (Sillanaukee and Olsson, 2001; Anttila *et al.*, 2003). As the current intoxication level is important information with potential treatment consequences (Savola *et al.*, 2004), blood alcohol should be measured in patients with suspected alcohol-related seizures (GPP).

Recommendation

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

Table 1 Early (< 72 h) post-ictal signs and symptoms after seizures because of epilepsy and alcohol withdrawal seizures

	Epilepsy	Early alcohol withdrawal
Consciousness level	Post-ictal sleep/drowsiness	Sleeplessness
Mood	Calm	Anxiety, unrest, nightmares
Tremor	No	Yes
Sweating	No	Yes
Blood pressure	Normal	Elevated
Pulse rate	Normal	Elevated (>90)
Temperature	Normal/light fever	Fever
Arterial blood	Normal	Respiratory alkalosis ^a
EEG	Pathology ^b	Normal, low amplitude
Questionnaires	Normal scores	Normal or elevated scores

^aRespiratory alkalosis may be masked by seizure-induced metabolic acidosis, but it will reappear within 2 h after cessation of convulsions (Orringer *et al.*, 1977); ^bInitial post-ictal slowing in most patients. Inter-ictal epileptiform discharges in approximately 50% (FIRST Group, 1993).

Patient examination and observation

The clinical examination should be focused on features distinctive of either epilepsy or withdrawal seizures (Table 1). To predict the severity of alcohol withdrawal, the revised Clinical Institute Withdrawal Assessment Scale (CIWA-Ar) can be applied (Sullivan *et al.*, 1989). 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 <http://www.efns.org>). More than 90% of alcohol withdrawal seizures (AWS) occur within 48 h of cessation of a prolonged drinking bout (Victor and Brausch, 1967; Bråthen *et al.*, 1999). 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 recent guidelines on the topic [Mayo-Smith *et al.*, 1997; Claassen and Adinoff, 1999; Scottish Intercollegiate Guidelines Network (SIGN), 2002; Mayo-Smith *et al.*, 2004].

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).

Neuroimaging

The diagnostic yield of cerebral computed tomography (CT) after a first alcohol-related seizure is high, mainly because patients overusing alcohol have a high incidence of structural intracranial lesions (Earnest *et al.*,

1988; Schoenenberger and Heim, 1994). Seizures that occur later than 48 h after intake of the last drink may indicate other potential aetiologies than simple alcohol withdrawal, such as subdural haematoma, brain contusion, or mixed drug and alcohol overuse (Hillbom and Hjelm-Jäger, 1984). When patients present repeatedly with clinically typical alcohol-related seizures, re-imaging is not necessary, but changes in seizure type and frequency, seizure occurrence more than 48 h after cessation of drinking, or other unusual features should prompt repeat neuroimaging (GPP).

Recommendation

Although it may seem obvious that a given seizure is alcohol-related, if it is a first known seizure, the patient should have brain imaging (CT or MRI) without and with contrast (level C recommendation).

Electroencephalography

The incidence of electroencephalography (EEG) abnormalities (slow or epileptiform activity) is lower amongst patients with 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 (Victor and Brausch, 1967; Sand *et al.*, 2002).

Recommendation

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).

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 (Torvik *et al.*, 1982; Blansjaar and van Dijk, 1992). The majority (approximately 80%) of those who show CNS lesions caused by thiamine deficiency are chronic alcohol overusers (Torvik *et al.*, 1982; Harper *et al.*, 1986).

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 (Holzbach, 1996). 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 (Ambrose *et al.*, 2001), from which it could only be concluded that a daily dose of 200 mg thiamine was better than 5 mg (Day *et al.*, 2004). 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

Because of large fluid intake (beer), hyponatremia 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 (Lampl and Yazdi, 2002). Hyponatremia in alcohol overusers generally shows a benign clinical course (Mochizuki *et al.*, 2003), and usually repairs with cessation of alcohol intake and re-institution of a normal diet (Kelly *et al.*, 1998). If infusion is considered necessary, according to a retrospective study the rate of serum sodium correction should not exceed 10 mmol/day (Saeed *et al.*, 2002). The evidence is insufficient for treatment recommendations.

Hypomagnesemia and respiratory alkalosis seem to be associated with alcohol withdrawal, and correction of hypomagnesemia may raise the seizure threshold in the initial phase of alcohol withdrawal (Victor, 1973). Unresponsiveness to parenteral thiamine therapy is a possible consequence of hypomagnesemia (Traviesa, 1974). However, there is not sufficient evidence to recommend routine correction of hypomagnesemia.

Should all patients with symptoms of alcohol withdrawal be offered seizure prophylactic treatment?

Patients with mild-to-moderate alcohol withdrawal symptoms (CIWA < 10) can successfully be detoxified with supportive care only (Whitfield *et al.*, 1978).

Supportive treatment includes a calm, reassuring atmosphere, dim light, coffee restriction, and hydration.

The mean incidence of seizures in patients receiving placebo during trials on drugs for prevention of AWS is approximately 8% (Hillbom *et al.*, 2003). These data originate from selected patients in need of treatment for alcoholism; the general seizure risk during uncomplicated alcohol withdrawal is probably lower. As seizures during previous detoxifications increase the risk for seizures during subsequent withdrawals (Lechtenberg and Worner, 1990; Mayo-Smith and Bernard, 1995), patients with these characteristics will probably benefit from prophylactic treatment regardless of the current withdrawal symptom severity.

Recommendation

For patients with no history of withdrawal seizures and mild to moderate withdrawal symptoms, routine seizure preventive treatment is not recommended (level B recommendation). Patients with severe alcohol withdrawal symptoms, regardless of seizure occurrence, should be treated pharmacologically (level C recommendation).

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 a meta-analysis of controlled trials for primary prevention of AWS, a highly significant risk reduction for seizures with BZD compared with placebo was demonstrated (Hillbom *et al.*, 2003). 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 because of BZD withdrawal and reducing rebound withdrawal symptoms after discontinuation, long-acting drugs should be preferred to short-acting ones (Mayo-Smith, 1997; Hillbom *et al.*, 2003). 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 (Saitz *et al.*, 1994; Jaeger *et al.*, 2001).

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. Many other drugs and drug combinations are being used, including carbamazepine, chlormethiazole, sodium valproate, gamma-hydroxybutyrate, and clonidine, all for which the documentation is generally poor (Robinson *et al.*, 1989; Saitz *et al.*, 1994; Holbrook *et al.*, 1999; Hillbom *et al.*, 2003).

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% (Hillbom *et al.*, 2003). 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 (D'Onofrio *et al.*, 1999). Phenytoin did not prevent relapses in patients who had one or more seizures during the same withdrawal episode (Hillbom *et al.*, 2003).

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 (Allredge and Lowenstein, 1993), it increases the risk for subsequent epilepsy (Hesdorffer *et al.*, 1998). One recent study indicates that lorazepam may be superior to

diazepam for the treatment of out-of-hospital SE (Allredge *et al.*, 2001). In another study comparing four treatments, lorazepam was considered easier to use but not more efficacious than diazepam, phenobarbital or phenytoin (Treiman *et al.*, 1998).

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 AEDs. Prescription of AEDs to alcohol overusers is often a fruitless undertaking which may increase their seizure problems because of poor compliance, drug overuse and drug-alcohol interactions (Hillbom and Hjelm-Jäger, 1984). 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 (Malcolm *et al.*, 2001), and have a suppressive effect on drinking behaviour. In a few small studies, carbamazepine, valproic acid and gabapentin have each been reported to reduce alcohol consumption (Mueller *et al.*, 1997; Brady *et al.*, 2002; Voris *et al.*, 2003), and topiramate has recently been shown to reduce craving for alcohol (Johnson *et al.*, 2003). 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 (Höppener, 1990). Only one randomized controlled clinical study (Höppener *et al.*, 1983) has addressed this particular issue; an intake of one to three drinks each containing 9.8 g ethanol (standard alcohol units; see Turner, 1990) 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 (Mattson *et al.*, 1990).

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 (Pedersen and Petersen, 1998).

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).

These guidelines will be updated when necessary and in any case within 4 years.

Conflicts of interest

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

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