CHAPTER 29
Alcohol-related seizures

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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'.

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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).

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. 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).

Biomarkers

For detection of alcohol overuse, questionnaire-based interviews are reported to be more sensitive than any biomarker [18, 19]. 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 [20, 21].

Carbohydrate-deficient transferrin (CDT) and gammaglutamyl 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 GT 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).

Table 29.1 Early (<72 h) post-ictal signs and symptoms after seizures due to 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

[a]Respiratory alkalosis may be masked by seizure-induced metabolic acidosis, but it will reappear within 2 h after cessation of convulsions ([29]).
[b]Initial post-ictal slowing in most patients. Interictal epileptiform discharges in approximately 50% ([28]).

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 [36, 37]. 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 [38]. 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 (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].

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 [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 reinstitution 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 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 [52]. 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% [53]. 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 [54, 55], 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 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 chlormethiazole, 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

1. Lloyd G. *Hippocratic Writings*. Middlesex, UK: Penguin Books, 1978; p. 222.
2. Earnest MP, Yarnell P. Seizure admissions to a city hospital: the role of alcohol. *Epilepsia* 1976;**17**:387–93.
3. Hillbom ME. Occurrence of cerebral seizures provoked by alcohol abuse. *Epilepsia* 1980;**21**:459–66.
4. Bråthen G, Brodtkorb E, Helde G, Sand T, Bovim G. The diversity of seizures related to alcohol use. A study of consecutive patients. *Eur J Neurol* 1999;**6**:697–703.
5. Jallon P, Smadja D, Cabre P, Le Mab G, Bazin M. EPIMART: prospective incidence study of epileptic seizures in newly referred patients in a french caribbean island (Martinique). *Epilepsia* 1999;**40**:1103–9.
6. Leone MA, Bråthen G. Treatment policies for alcohol-related seizures: a survey of European neurologists. *Eur J Neurol* 2007;**14**(3):e2–3.
7. Bråthen G, Ben-Menachem E, Brodtkorb E, *et al*. EFNS Guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force. *Eur J Neurol* 2005;**12**:575–81.
8. Brainin M, Barnes M, Baron J-C, *et al*. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations. *Eur J Neurol* 2004;**11**:577–81.
9. Mayfield D, Mcleod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry* 1974;**131**(10):1121–3.
10. Matano RA, Koopman C, Wanat SF, Whitsell SD, Borgrefe A, Westrup D. Assessment of binge drinking of alcohol in highly educated employees. *Addict Behav* 2003;**28**: 1299–310.
11. Fiellin DA, Reid MC, O'Connor PG. Screening for alcohol problems in primary care: a systematic review. *Arch Intern Med* 2000;**160**(13):1977–89.
12. MacKenzie D, Langa A, Brown T. Identifying hazardous or harmful alcohol use in medical admissions: a comparison of Audit, CAGE and Brief MAST. *Alcohol Alcohol* 1996; **31**:591–9.
13. Bush K, Kivlahan DR, McDonnel MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Arch Intern Med* 1998;**16**:1789–95.
14. Hodgson RJ, John B, Abbasi T, *et al*. Fast screening for alcohol misuse. *Addict Behav* 2003;**28**:1453–63.
15. Piccinelli M, Tessari E, Bortolomasi M, *et al*. Efficacy of the alcohol use disorders identification test as a screening tool for hazardous alcohol intake and related disorders in primary care: a validity study. *BMJ* 1997;**314**:420–7.
16. Seppa K, Lepisto J, Sillanaukee P. Five-shot questionnaire on heavy drinking. *Alcohol Clin Exp Res* 1998;**22**(8):1788–91.
17. Feuerlein W, Ringer C, Kufner H, Antons K. Diagnose des Alkoholismus. Der Münchner Alkoholismustest (MALT). *Munch Med Wschr* 1977;**119**:1275–86.
18. Aertgeerts B, Buntinx F, Ansoms S, Fevery J. Questionnaires are better than laboratory tests to screen for current alcohol abuse or dependence in a male inpatient population. *Acta Clin Belg* 2002;**57**:241–9.
19. Bernadt MW, Mumford J, Taylor C, Smith B, Murray RM. Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet* 1982;**i**:325–8.
20. Bråthen G, Bjerve K, Brodtkorb B, Bovim G. Validity of carbohydrate-deficient transferrin and other markers as diagnostic aids in the detection of alcohol-related seizures. *J Neurol Neurosurg Psychiatry* 2000;**68**:342–8.
21. Martin MJ, Heyermann C, Neumann T, *et al*. Preoperative evaluation of chronic alcoholics assessed for surgery of

the upper digestive tract. *Alcohol Clin Exp Res* 2002; **26**:836–40.
22. Salaspuro M. Carbohydrate-deficient transferrin as compared to other markers of alcoholism: a systematic review. *Alcohol* 1999;**19**(3):261–71.
23. Scouller K, Conigrave KM, Macaskill P, Irwig L, Whitfield JB. Should we use carbohydrate-deficient transferrin instead of G-glutamyltransferase for detecting problem drinkers? A systematic review and metaanalysis. *Clin Chem* 2000;**46**: 1894–902.
24. Hietala J, Koivisto H, Anttila P, Niemelä O. Comparison of the combined marker GGT-CDT and the conventional laboratory markers of alcohol abuse in heavy drinkers, moderate drinkers and abstainers. *Alcohol Alcohol* 2006; **41**:528–33.
25. Bentele M, Kriston L, Clement HW, Härter M, Mundle G, Berner MM. The validity of the laboratory marker combinations DOVER and QUVER to detect physician's diagnosis of at-risk drinking. *Addict Biol* 2007;**12**:85–92.
26. Sillanaukee P, Olsson U. Improved diagnostic classification of alcohol abusers by combining carbohydrate-deficient transferrin and G-glutamyltransferase. *Clin Chem* 2001; **47**:681–5.
27. Savola O, Niemelä O, Hillbom M. Blood alcohol is the best indicator of hazardous alcohol drinking in young adults and working aged patients with trauma. *Alcohol Alcohol* 2004; **39**:340–5.
28. FIRST Group. Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology* 1993;**43**: 478–83.
29. Orringer CE, Eustace JC, Wunsch CD, Gardner LB. Natural history of lactic acidosis after grand-mal seizures. A model for the study of an anion-gap acidosis not associated with hyperkalemia. *N Engl J Med* 1977;**297**:796–9.
30. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-AR). *Br J Addict* 1989;**84**:1353–7.
31. Victor M, Brausch C. The Role of Abstinence in the Genesis of Alcoholic Epilepsy. *Epilepsia* 1967;**8**:1–20.
32. Claassen CA, Adinoff B. Alcohol withdrawal syndrome. Guidelines for management. *CNS Drugs* 1999;**12**:279–91.
33. Mayo-Smith MF for the American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. *JAMA* 1997;**278**:144–51.
34. Mayo-Smith MF, Beecher LH, Fischer TL, *et al*. for the Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 2004;**164**:1405–12.
35. Scottish Intercollegiate Guidelines Network (SIGN). *The Management of Harmful Drinking and Alcohol Dependence in Primary Care*. Edinburgh: SIGN, 2002; (SIGN publication No. 74).
36. Earnest MP, Feldman H, Marx JA, Harris BS, Biletch M, Sullivan LP. Intracranial lesions shown by CT in 259 cases of first alcohol related seizure. *Neurology* 1988;**38**:1561.
37. Schoenenberger RA, Heim SM. Indication for computed tomography of the brain in patients with first uncomplicated generalised seizure. *BMJ* 1994;**309**:986–9.
38. Hillbom ME, Hjelm-Jaeger M. Should alcohol withdrawal seizures be treated with anti-epileptic drugs? *Acta Neurol Scand* 1984;**69**:39–2.
39. Sand T, Bråthen G, Michler R, Brodtkorb E, Helde G, Bovim G. Clinical utility of EEG in alcohol-related seizures. *Acta Neurol Scand* 2002;**105**:18–24.
40. Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics: a neuropathological study with clinical correlations. *J Neurol Sci* 1982;**56**:233–48.
41. Blansjaar BA, Van Dijk JG. Korsakoff-Wernicke syndrome. *Alcohol Alcohol* 1992;**27**:435–7.
42. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. *J Neurol Neurosurg Psychiatry* 1986;**49**:341–5.
43. Holzbach E. Thiamine absorption in alcoholic delirium patients. *J Studies Alcohol* 1996;**57**:581–4.
44. Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. *Alcohol Clin Exp Res* 2001; **25**:112–6.
45. Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse. *Cochrane Database of Systematic Reviews* 2004;(1):Art. No.: CD004033. DOI: 10.1002/14651858.CD004033.pub2.
46. Lampl C, Yazdi K. Central pontine myelinolysis. *Eur Neurol* 2002;**47**(1):3–10.
47. Mochizuki H, Masaki T, Miyakawa T, *et al*. Benign type of central pontine myelinolysis in alcoholism: clinical, neuroradiological and electrophysiological findings. *J Neurol* 2003;**250**:1077–83.
48. Kelly J, Wassif W, Mitchard J, Gardner WN. Severe hyponatremia secondary to beer potomania complicated by central pontine myelinolysis. *Int J Clin Pract* 1998;**52**:585–7.
49. Saeed BO, Beaumont D, Handley GH, Weaver JU. Severe hyponatremia: investigation and management in a district general hospital. *J Clin Pathol* 2002;**55**:893–6.

50. Victor M. The role of hypomagnesemia and respiratory alkalosis in the genesis of alcohol withdrawal symptoms. *Ann NY Acad Sci* 1973;**215**:235–48.
51. Traviesa DC. Magnesium deficiency: a possible cause of thiamine refractoriness in Wernicke-Korsakoff encephalopathy. *J Neurol Neurosurg Psychiatry* 1974;**37**:959–62.
52. Whitfield CL, Thompson G, Lamb A, Spencer V, Pfeifer M, Browning-Ferrando M. Detoxification of 1,024 alcoholic patients without psychoactive drugs. *JAMA* 1978;**239**(14): 1409–10.
53. Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients. Epidemiology, pathophysiology and management. *CNS Drugs* 2003;**17**:1013–30.
54. Lechtenberg R, Worner T. Seizure risk with recurrent alcohol detoxification. *Arch Neurol* 1990;**47**:535–8.
55. Mayo-Smith MF, Bernard D. Late onset seizures in alcohol withdrawal. *Alcohol Clin Exp Res* 1995;**19**:656–9.
56. Ntais C, Pakos E, Kyzas P, Ioannidis JP. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev* 2005;(3):Art. No.: CD005063. DOI: 10.1002/14651858. CD005063.pub2.
57. Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. *JAMA* 1994;**272**:519–23.
58. Jaeger TM, Lohr RH, Pankratz VS. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. *Mayo Clin Proc* 2001;**76**:695–701.
59. Polycarpou A, Papanikolau P, Ionannidis JPA, Contopoulos Ioannidis D. Anticonvulsants for alcohol withdrawal. *Cochrane Database Syst Rev* 2005;(3):Art. No.: CD005064. DOI: 10.1002/14651858.CD005064.pub2.
60. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. *CMAJ* 1999;**160**:649–55.
61. Robinson BJ, Robinson GM, Maling TJ, Johnson RH. Is clonidine useful in the treatment of alcohol withdrawal? *Alcohol Clin Exp Res* 1989;**13**:95–8.
62. D'Onofrio G, Rathlev NK, Ulrich AS, Fish SS, Freedland ES. Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999;**340**:915–9.
63. Alldredge BK, Lowenstein DH. Status epilepticus related to alcohol abuse. *Epilepsia* 1993;**34**:1033–7.
64. Hesdorffer DC, Logroscino G, Cascino G, *et al*. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998;**44**:908–12.
65. Alldredge BK, Gelb AM, Isaacs SM, *et al*. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;**345**: 631–7.
66. Treiman DM, Meyers PD, Walton NY, *et al*. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;**339**:792–8.
67. Malcolm R, Myrick H, Brady KT, Ballenger JC. Update on anticonvulsants for the treatment of alcohol withdrawal. *Am J Addict* 2001;**10**(Suppl.):16–23.
68. Mueller TI, Stout RL, Rudden S, *et al*. A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997;**21**(1):86–92.
69. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res* 2008;**32**(8):1429–38.
70. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry* 2005; **62**(1):37–45.
71. Martinotti G, Di Nicola M, Tedeschi D, Mazza M, Janiri L, Bria P. Efficacy and safety of pregabalin in alcohol dependence. *Adv Ther* 2008;**25**(6):608–18.
72. Johnson BA, Rosenthal N, Capece JA, *et al*. Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007;**298**(14): 1641–51.
73. Höppener RJ. The effect of social alcohol use on seizures in patients with epilepsy. In: Porter RJ, Mattson RH, Cramer JA, Diamond I (eds) *Alcohol and Seizures. Basic Mechanisms and Clinical Concepts*. Philadelphia: F.A. Davis Company, 1990; pp. 222–32.
74. Höppener RJ, Kuyer A, van der Lugt PJM. Epilepsy and alcohol: the influence of social alcohol intake on seizures and treatment in epilepsy. *Epilepsia* 1983;**24**: 459–71.
75. Turner C. How much alcohol is in a 'standard drink'? An analysis of 125 studies. *Br J Addict* 1990;**85**:1171–5.
76. Mattson RH, Fay ML, Sturman JK, Cramer JA, Wallace JD, Mattson EM. The effect of various patterns of alcohol use on seizures in patients with epilepsy. In: Porter RJ, Mattson RH, Cramer JA, Diamond I (eds) *Alcohol and Seizures. Basic Mechanisms and Clinical Concepts*. Philadelphia: F.A. Davis Company, 1990; pp. 233–40.
77. Pedersen SB, Petersen KA. Juvenile myoclonic epilepsy: clinical and EEG features. *Acta Neurol Scand* 1998;**97**: 160–3.