臨床問題敘述(Problem description):
Are benzodiazepines and anticonvulsants effective for patient with alcohol withdrawal symptoms? (Are anticonvulsants more effective than benzodiazepines?)
P: alcohol withdrawal
I: benzodiazepines and anticonvulsants
C: placebo or active placebo
O: prevent or relief alcohol symptoms (ex: delirium, seizure), prevent re-intake alcohol

關鍵字(Key words):
alcohol withdrawal and benzodiazepine, alcohol withdrawal and anticonvulsants

資料庫搜尋敘述(Literature search):
PubMed: 106 papers (alcohol withdrawal and benzodiazepine)
186 papers (alcohol withdrawal and anticonvulsants)
Medline: 244 papers (alcohol withdrawal and benzodiazepine)
120 papers (alcohol withdrawal and anticonvulsants)
Cochrane: 1 papers (alcohol withdrawal and benzodiazepine)
1 papers (alcohol withdrawal and anticonvulsants)

參考文獻摘要與等級
   Benzodiazepines, especially diazepam and chlordiazepoxide, are the drugs of choice. Barbiturates, beta-blockers, and antipsychotics are generally not recommended as first-line therapy. carbamazepine and clonidine, have been shown to be about as effective as benzodiazepines in a few studies, but the studies were small. beta-blockers, may play a role as adjuncts to, not replacements for, benzodiazepine therapy.

   Benzodiazepines reduce withdrawal severity, reduce incidence of delirium (P=.04), and reduce seizures (P=.003), significantly less medication and shorter treatment (P<.001). beta-Blockers, clonidine, and carbamazepine ameliorate withdrawal severity, but evidence is inadequate to determine their effect on delirium and seizures. Benzodiazepines are suitable agents for alcohol withdrawal, with choice among different agents guided by duration of action, rapidity of onset, and cost. Dosage should be individualized, based on withdrawal severity measured by withdrawal scales, comorbid illness, and history of withdrawal seizures. beta-Blockers, clonidine, carbamazepine, and neuroleptics may be used as adjunctive therapy but are not recommended as monotherapy.

The meta-analysis of benefit (therapeutic success within 2 days) showed that benzodiazepines were superior to placebo (OR 3.28, 95% CI 1.30–8.28), none of the alternative drugs (β-blockers, carbamazepine and clonidine) was found to be clearly more beneficial than the benzodiazepines. No significant difference between benzodiazepines and alternative drugs in terms of adverse events (common OR 0.67, 95% CI 0.34–1.32) or dropout rates (common OR 0.68, 95% CI 0.47–0.97). Benzodiazepines should remain the drugs of choice for the treatment of acute alcohol withdrawal.

Meta-analysis of 9 prospective controlled trials demonstrated that sedative-hypnotic agents are more effective than neuroleptic agents in reducing duration of delirium and mortality, with a relative risk of death when using neuroleptic agents of 6.6. Statistically significant differences among various benzodiazepines and barbiturates were not found. No deaths were reported in 217 patients from trials using benzodiazepines or barbiturates.

In patients with alcohol withdrawal delirium, sedative-hypnotic drugs reduce mortality and duration of delirium more than neuroleptic drugs, with no differences among different sedative-hypnotic drugs.

Main results
Benzodiazepines offered a large benefit against alcohol withdrawal seizures compared to placebo (relative risk [RR] 0.16; 95% confidence interval [CI] 0.04 to 0.69; p = 0.01). Benzodiazepines had similar success rates as other drugs (RR 1.00; 95% CI 0.83 to 1.21) or anticonvulsants in particular (RR 0.88; 95% CI 0.60 to 1.30) and offered a significant benefit for seizure control against nonanticonvulsants (RR 0.23; 95% CI 0.07 to 0.75; p = 0.02), but not against anticonvulsants (RR 1.99; 95% CI 0.46 to 8.65). Changes in Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scores at the end of treatment were similar with benzodiazepines versus other drugs.
Authors' conclusions
Benzodiazepines are effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo. It is not possible to draw definite conclusions about the relative effectiveness and safety of benzodiazepines against other drugs in alcohol withdrawal, because of the large heterogeneity of the trials both in interventions and assessment of outcomes but the available data do not show prominent differences between benzodiazepines and other drugs in success rates.

This placebo-controlled pilot study suggests that divalproex sodium significantly affects the course of acute alcohol withdrawal and reduces the need for treatment with a benzodiazepine. A more aggressive loading dose strategy may demonstrate a more robust or
earlier response.


This review confirms that valproic acid should not replace benzodiazepines for prevention and treatment of AWS. Valproic acid may affect the severity of symptoms and the benzodiazepine requirements in alcoholics with mild-to-moderate withdrawal. However, the benefits appear negligible, and their clinical importance is debatable. The safety and optimal dose of valproic acid for management of AWS remain unknown.

valproic acid should not replace conventional therapy or be used as adjunct therapy for management of mild-to-moderate AWS


Statistical significance was reached regarding the positive relationship between prior ethanol use and inpatient "as needed" benzodiazepine use. Both sets of data suggest that gabapentin works well for the mild to moderate alcohol withdrawal patient.


Both benzodiazepines and tiagabine appeared to reduce CIWA-Ar scores at about the same magnitude. There was a trend for tiagabine patients to have less post-detoxification drinking (Fisher exact test, p = 0.12). The reduction in alcohol withdrawal symptoms and decreased tendency to relapse observed in patients treated with the anticonvulsant tiagabine suggests that a double-blind, placebo controlled trial may be warranted.


Non-benzodiazepine anticonvulsants such as carbamazepine, valproic acid, gabapentin, vigabatrin and topiramate have been shown to be excellent treatments of both alcohol withdrawal and the prevention of alcohol relapse. Although none of these agents have yet been approved by the FDA, there is growing evidence in the literature to support their use.


A number of anticonvulsants including valproate and carbamazepine have been shown to be safe and effective alternatives to benzodiazepines for treating alcohol withdrawal. These agents are relatively safe, are free from demonstrated abuse liability, and do not usually potentiate the psychomotor and cognitive effects of alcohol.

13. Polycarpou A, Papanikolaou P, Ioannidis JPA, Contopoulos-Ioannidis DG

Anticonvulsants for alcohol withdrawal. The Cochrane database of systematic reviews, 2006, Issue 1. (1 A)

Forty-eight studies, involving 3610 people were included. Despite the considerable number of randomized controlled trials, there was a variety of outcomes and of different rating scales that led to a limited quantitative synthesis of data. For the anticonvulsant versus placebo comparison, therapeutic success tended to be more common among the anticonvulsant-treated patients (relative risk (RR) 1.32; 95% confidence interval (CI) 0.92 to 1.91), and anticonvulsant tended to show a protective benefit against seizures (RR 0.57; 95% CI 0.27 to 1.19), but no effect reached formal statistical significance. For the anticonvulsant versus other drug comparison, CIWA-Ar score showed non-significant differences for the anticonvulsants compared to the other drugs at the end of treatment (weighted mean difference (WMD) -0.73; 95% CI -1.76 to 0.31). For the subgroup analysis of carbamazepine versus benzodiazepine, a statistically significant protective effect was found for the anticonvulsant (WMD -1.04; 95% CI -1.89 to -0.20), but this was based on only 260 randomized participants. There was a non-significant decreased incidence of seizures (RR 0.50; 95% CI 0.18 to 1.34) favouring the patients that were treated with anticonvulsants than other drugs, and side-effects tended to be less common in the anticonvulsant-group (RR 0.56; 95% CI 0.31 to 1.02).
**Authors' conclusions**

It is not possible to draw definite conclusions about the effectiveness and safety of anticonvulsants in alcohol withdrawal, because of the **heterogeneity of the trials** both in interventions and the assessment of outcomes. The extremely small mortality rate in all these studies is reassuring, but data on other safety outcomes are sparse and fragmented.


Carbamazepine and lorazepam were both effective in decreasing the symptoms of alcohol withdrawal in relatively healthy, middle-aged outpatients. **Carbamazepine, however, was superior to lorazepam in preventing rebound withdrawal symptoms and reducing post-treatment drinking, especially for those with a history of multiple treated withdrawals.**

**結論(Reviewers' conclusions):**

1. benzodiazepine and anticonvulsants are effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo.
2. Benzodiazepines had **similar success rates as other drugs or anticonvulsants**
3. non-significant differences for the anticonvulsants compared to the other drugs at the end of treatment (CIWA-Ar score)
4. carbamazepine shown to be safe and effective alternatives to benzodiazepines for treating alcohol withdrawal. (reducing post-treatment drinking and BZDs abuse)

**臨床應用(Clinical practice)與現況分析:**

1. Benzodiazepines: first-line drug therapy for the management of acute alcohol withdrawal. (lorazepam, diazepam, clonazepam)
2. add anticonvulsants (carbamazepine, valproic acid) if patient comorbid with seizure attack or psychiatric disease (bipolar disorder or mood irritable)

**種子教師意見:**