Q3: In the treatment of alcohol withdrawal delirium, are benzodiazepines or antipsychotics safe and effective when compared to a placebo/appropriate comparator to produce benefit/harm in the specified outcomes?

Background

Alcohol withdrawal delirium (AWD), commonly known as delirium tremens is the most serious manifestation of alcohol withdrawal syndrome. The classic clinical presentation of AWD includes hyperpyrexia, tachycardia, hypertension, and diaphoresis. The incidence of AWD averages 5% in placebo-treated alcohol dependent patients entered into clinical trials of inpatient drug treatment for alcohol withdrawal (Mayo-Smith 1997). Clinical features of alcohol withdrawal syndrome can appear within hours of the last drink, but delirium typically does not develop until 2 to 3 days after cessation of drinking. Alcohol withdrawal delirium usually lasts 48 to 72 hours (Stendig-Lindberg & Rudy, 1980; Cutshall 1965; Victor & Adams, 1953), but there have been case reports of much longer duration. Initial studies found mortality to be as high as 15% (Victor & Adams, 1953), but with advances in treatment, mortality rates have fallen, with more recent studies indicating mortality of 0% to 1%.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	patients with alcohol withdrawal delirium
Interventions:	sedative-hypnotic or antipsychotic medications
Comparison:	placebo/comparator
Outcomes:	control of alcohol withdrawal delirium
	mortality
	adverse effects of medication (where appropriate) and their compliance

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Mayo-Smith et al (2004). 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. *Archives of Internal Medicine,* 12; 164:1405-12.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	sedative-hypnotic / antipsychotic medications	Mortality *Treatment complications*	Mayo-Smith et al, 2004	5 controlled trials *1 study (*Kaim & Klett, 1972)

Narrative description of the studies that went into the analysis

Friedhoff & Zitrin, 1959 compared the effects of paraldehyde and chlorpromazine in delirium tremens.

Thomas & Freedman, 1964 compared promazine and paraldehyde for the treatment of alcohol withdrawal syndrome. A total of 106 patients were treated in this study, 51 with promazine hydrochloride and 55 with paraldehyde. Significantly more deaths occurred in those treated with promazine hydrochloride than in those treated with paraldehyde. For most patients with mild withdrawal, symptoms cleared more rapidly with promazine. Paraldehyde was more efficacious in the delirium tremens group.

Chambers & Schultz, 1965 conducted a double-blind study of three drugs in the treatment of acute alcoholic states (promazine + chloral hydrate, diazepam, chlordiazepoxide)

Golbert et al, 1967 completed a clinical comparative study, where 49 patients were treated for the tremulous and agitated states and acute hallucinosis of alcohol withdrawal. Thirteen patients were treated with promazine hydrochloride, and 12 each with paraldehyde and chloral hydrate, alcohol, or chlordiazepoxide hydrochloride. Of these therapies, paraldehyde with chloral hydrate was most effective and best tolerated. Twenty-three patients were treated for delirium tremens. Twelve were treated with promazine and suffered numerous complications, including death in two cases. Eleven were treated with paraldehyde and chloral hydrate with prompt clearing of hallucinations; there were no failures and only one complication (transient fever).

Kaim & Klett, 1972 compared four drugs for the treatment of delirium tremens due to AWD (perphenazine, chlordiazepoxide, pentobarbital, and diazepam).

GRADE Tables

Table 1

Author(s): Clark N
Date: 2009-09-18
Question: Should antipsychotic vs. sedative hypnotic medication be used for alcohol withdrawal delirium?
Settings:
Bibliography: Mayo-Smith MF et al (2004). Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Archives of Internal Medicine*. 164:1405-12.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antipsychotics	sedative-hypnotics	Relative (95% CI)	Absolute		
Mortality (Relative risk)												
5	randomized trials	no serious limitations	serious[1]	no serious indirectness[2]	serious[3]	none	8/125 (6.4%)	1/220 (0.5%)	RR 6.6 (1.2 to 34.7)	25 more per 1000 (from 1 more to 153 more)	LOW	CRITICAL
								0%		0 more per 1000 (from 0 more to 0 more)		
Treatment severe complications												
1[4]	randomized trials	no serious limitations	serious[5]	no serious indirectness	serious[6]	none	0/46 (0%)	0/101 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] I square was not calculated but there is the appearance of imprecision.
[2] All studies included alcohol withdrawal syndrome.
[3] Upper confidence limit crosses 2.
[4] Kaim & Klett, 1972
[5] Single study
[6] Neuroleptic=46; sedative-hypnotic=147. There were no complications reported for these medications.

Additional information that was not GRADEd

DURATION OF DELIRIUM

Three trials (Friedhoff & Zitrin, 1959; Thomas & Freedman, 1964; Kaim & Klett, 1972) comparing sedative-hypnotic agents with antipsychotic agents demonstrated that the former are superior to the latter in reducing the duration of AWD. (In the Golbert et al, 1967 study, there was insufficient data in the original article to calculate P values.) Differences among sedative-hypnotic agents in reducing duration of AWD were not demonstrated.

None of these studies considered the time required to control agitation.

ADEQUATE CONTROL OF DELIRIUM

In a large, multicenter Veterans Affairs study (Kaim & Klett, S1972), there were no significant differences in achieving adequate control of delirium, but the rate of failure was low. Two of 46 patients taking perphenazine and 1 of 41 taking pentobarbital were "unresponsive to treatment" with their assigned medication. Studies have demonstrated that the required dose of medication can vary substantially among patients and within the same patient over time.

Reference List

Chambers JF, Schultz JD (1965). Double-blind study of three drugs in the treatment of acute alcoholic states. *Quarterly Journal of Studies on Alcohol,* 26:10-18.

Cutshall BJ (1965). The Saunderssutton syndrome: an analysis of delirium tremens. *Quartely Journal of Studies on Alcohol,* 26:423-48.

Friedhoff AJ, Zitrin A (1959). A comparison of the effects of paraldehyde chlorpromazine in delirium tremens. *New York State Journal of Medicine,* 59:1060-3.

Golbert TM et al (1967). Comparative evaluation of treatments of alcohol withdrawal syndromes. *Journal of the American Medical Association,* 201:99-102.

Kaim SC, Klett CJ (1972). Treatment of delirium tremens. A comparative evaluation of four drugs. *Quarterly Journal of Studies on Alcohol,* 33:1065-72.

Mayo-Smith MF (1997). Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *Journal of American Medical Association,* 278:144-51.

Mayo-Smith MF et al (2004). Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Archives of Internal Medicine,* 164:1405-12.

Stendig-Lindberg G, Rudy N (1980). Stepwise regression analysis of an intensive 1-year study of delirium tremens. Acta Psychiatrica Scandinavaca, 62:273-97.

Thomas DW, Freedman DX (1964). Treatment of alcohol withdrawal syndrome. Comparison of promazine and paraldehyde. *Journal of the American Medical Association,* 188:316-8.

Victor M, Adams RD (1953). The effect of alcohol on the nervous system. *Research Publications - Association for Research in Nervous and Mental Disease,* 32:526-73.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	Meta-analysis of 5 studies indicated that antipsychotics have a higher mortality rate than sedative-hypnotics in the management of alcohol withdrawal delirium (RR 6.6 (1.2 to 34.7)). Sedative-hypnotic use was also shown to reduce the duration of the delirium and seems to control more adequately alcohol withdrawal delirium. No significant differences in severe treatment complications were reported between sedative-hypnotics and antipsychotics.
Summary of the quality of evidence	LOW
Balance of benefits versus harms	Rapid and adequate control of agitation reduces the incidence of clinically important adverse events. Antipsychotic agents have the potential to cause a variety of serious adverse effects, particularly when used in very high doses, which may be required to control severe agitation. Chlorpromazine, promazine, and other low-potency typical antipsychotic agents have been reported to have the greatest effect on lowering seizure threshold.
Define the values and preferences including any variability and human rights issues	Often patients with delirium are unable to care for themselves and need to be placed in a safe environment. Where possible, the most dignified measures should be taken to prevent patients leaving that safe environment.
Define the costs and resource use	Management of patients with delirium can be resource intensive. In some cases one to one nursing care is required, if patients

and any other relevant feasibility issues	are wandering and there are not family members to care for them.
Final recommendation(s) Benzodiazepines should be used for the treatment alcohol withdrawal delirium. Strength of recommendation: STRONG Antipsychotic medications should not be used as stand alone treatment for alcohol withdrawal delirium. Strength of recommendation: STRONG Antipsychotics should only be used as an adjunct to benzodiazepines in severe withdrawal delirium which has not responded to adequate doses of benzodiazepines. Strength of recommendation: STRONG	

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant.