

Management of alcohol withdrawal

Q2: What interventions are safe and effective for the management of alcohol withdrawal, including treatment for alcohol withdrawal seizures and prevention and treatment for acute Wernicke's encephalopathy?

Background

Alcohol withdrawal can be uncomfortable and occasionally life threatening. Pharmacological management of alcohol withdrawal is an essential component of alcohol dependence. Benzodiazepines (BZDs), non-sedating anticonvulsants and antipsychotics are commonly used in the treatment of alcohol withdrawal. Given that they are all potentially toxic medications, what is the evidence that the benefits of their use justify the risks? Which is more effective?

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

Population:	people with alcohol dependence commencing alcohol withdrawal
Interventions:	benzodiazepines anticonvulsants (non sedating i.e. non barbiturates and not chlormethiazole) antipsychotics
Comparison:	placebo and/or active treatment
Outcomes:	severity of withdrawal complications of withdrawal (seizures, delirium) completion of withdrawal death

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Ntais C et al (2005). Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Review*, (3):CD005063.

Polycarpou A et al (2005). Anticonvulsants for alcohol withdrawal. *Cochrane Database of Systematic Reviews*, (3):CD005064.

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.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Benzodiazepines vs. anticonvulsants	Withdrawal severity Alcohol withdrawal delirium Alcohol withdrawal seizures Completion of withdrawal Death	Ntais et al, 2005; Polycarpou et al, 2005	Cochrane reviews
2	Benzodiazepines vs. placebo or no treatment	Withdrawal severity Alcohol withdrawal delirium Alcohol withdrawal seizures Completion of withdrawal Death	Ntais et al, 2005	Cochrane review
3	Benzodiazepines vs. antipsychotics	Withdrawal severity Alcohol withdrawal delirium Alcohol withdrawal seizures Completion of withdrawal Death	Mayo-Smith, 1997; Ntais et al, 2005	More extensive review than the Cochrane review
4	Anticonvulsants vs. placebo or no treatment	Withdrawal severity Alcohol withdrawal delirium	Polycarpou et al, 2005	Cochrane review

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		Alcohol withdrawal seizures Completion of withdrawal Death		
5	Antipsychotics vs. placebo or no treatment	Withdrawal severity Alcohol withdrawal delirium Alcohol withdrawal seizures Completion of withdrawal Death	Mayo-smith, 1997	More extensive review than the Cochrane review

Narrative description of the studies that went into the analysis

Ntais et al, (2005): A search of the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to October 2004) and EU-PSI PSI-Tri database was conducted with no language and publication restrictions. References of retrieved articles were also screened. Selection criteria: All randomized controlled trials examining the effectiveness and safety of a benzodiazepine in comparison with a placebo or other pharmacological intervention or other benzodiazepine were considered. Data collection and analysis: Two reviewers independently assessed trial quality and extracted data. Main results: Fifty-seven trials, with a total of 4,051 people were included. Despite the considerable number of randomized controlled trials, there was a very large variety of outcomes and of different rating scales and relatively limited quantitative synthesis of data was feasible. 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 non- anticonvulsants (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, although some small studies showed isolated significant differences for other, less commonly, used scales. Data on other comparisons were very limited, thus making quantitative synthesis for various outcomes not very informative.

Polycarpou et al, (2005): The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2004); MEDLINE (1966 to October 2004); EMBASE (1988 to October 2004) and EU-PSI PSI-Tri database was searched with no language and publication restrictions and references of articles. Selection criteria: All randomized controlled trials examining the effectiveness, safety and overall risk-benefit of an anticonvulsant in comparison with a placebo or other pharmacological treatment or another anticonvulsant were considered. Main results: 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

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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), $p = 0.02$), 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).

Mayo-Smith (1997): Articles with original data on management of alcohol withdrawal delirium underwent structured review and meta-analysis. A meta-analysis of 9 prospective controlled trials demonstrated that sedative-hypnotic agents are more effective than neuroleptics agents in reducing duration of delirium and mortality, with a relative risk of death when using neuroleptics 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

NICE Guidelines (unpublished at the time of review)

The new NICE guidelines, not yet published, on the management of alcohol dependence have reviewed the evidence for the treatment of Wernicke's encephalopathy. There were no relevant randomized controlled trials.

GRADE tables

Table 1

Author(s): N Clark, N Lintzeris

Date: 2009-08-04

Question: Should benzodiazepines vs. anticonvulsants (not barbiturates) be used for alcohol withdrawal?

Settings:

Bibliography: Ntais C et al (2005). Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Review*, (3):CD005063.

Polycarpou A et al (2005). Anticonvulsants for alcohol withdrawal. *Cochrane Database of Systematic Reviews*, (3):CD005064.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	anticonvulsants (not barbiturates)	Relative (95% CI)	Absolute		
peak withdrawal severity (48 hrs) (follow-up 2 days; measured with: Mean CIWA-Ar score; range of scores: 0-67; Better indicated by lower values)												
3	randomized trials	serious ¹	no serious inconsistency ²	no serious indirectness ³	no serious imprecision	none	138 ⁴	122 ^{4,5}	-	MD 0.60 higher (0.67 lower to 1.88)	MODERATE	IMPORTANT

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										higher)		
alcohol withdrawal delirium												
2 ⁶	randomized trials	no serious limitations	serious ⁷	no serious indirectness	very serious ⁸	none	2/63 (3.2%)	2/62 (3.2%)	RR 0.99 (0.04 to 24.43)	0 fewer per 1000 (from 31 fewer to 756 more)	VERY LOW	CRITICAL
alcohol withdrawal seizures												
1 ⁹	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹⁰	none	1/29 (3.4%)	0/29 (0%)	RR 3.00 (0.13 to 70.74)	0 more per 1000 (from 0 fewer to 0 more)	LOW	
								2%		40 more per 1000 (from 17 fewer to 1395 more)		
completion of withdrawal												
2 ¹¹	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹²	none	10/73 (13.7%)	14/76 (18.4%)	RR 0.71 (0.29 to 1.72)	53 fewer per 1000 (from 131 fewer to 133 more)	LOW	IMPORTANT
death (follow-up mean 1 weeks)												
4 ¹³	randomized trials	serious ¹⁴	no serious inconsistency	no serious indirectness	very serious ¹⁵	none	0/172 (0%)	0/155 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL

¹ Main study (Malcolm et al, 2002) is OP design, but authors do not report alcohol consumption during treatment period. 65% of subjects reported drinking from day 7 onwards, suggesting a proportion may have been drinking during the treatment period.

² I squared = 21%.

³ Largest study (Malcolm et al, 2002) conducted in outpatient setting.

⁴ Drop outs not accounted for. In Malcolm et al, 2002, 17 of 136 subjects dropped out at day 2.

⁵ Drop outs not accounted for. In Malcolm et al, 2002, 17 of 136 subjects dropped out at day 2.

⁶ Analysis 2.6 Ntais et al 2005, Sub analysis 4 (carbamazepine only v benzodiazepine) (Lucht et al 2003 in subanalysis 3 includes tiapride + carbamazepine).

⁷ I squared = 56%.

⁸ Only n=4 events reported in total of n=125 subjects.

⁹ Stuppaeck et al, 1992 included. Other studies from Polycarpou et al, 2005 Cochrane review anticonvulsants excluded as they examine barbiturates or combination treatment in conjunction with anticonvulsants (Lucht et al, 2003).

¹⁰ Only 1 case event in single study of 58 subjects.

¹¹ New analysis based on Ntais et al, 2005 review analysis 2.15 including Kalyoncu et al, 1996; Stuppaeck et al, 1992, and excluding other studies which used anticonvulsants not considered here.

¹² Small studies with only a few events.

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¹³ From Ntais et al, 2005 analysis 2.16. Including Kalyoncu et al, 1996; Malcolm et al, 1989; Malcolm et al, 2002; Stuppaek et al, 1992, and other trials excluded as they used anticonvulsants not being considered here.

¹⁴ Patients who dropped out of treatment were not included in the analysis.

¹⁵ Studies underpowered to detect this rare outcome.

Table 2

Author(s): N Lintzeris, N Clark

Date: 2009-08-04

Question: Should benzodiazepines vs. placebo be used for alcohol withdrawal?

Settings:

Bibliography: 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.

Ntais C et al (2005). Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Review*, (3):CD005063.

Quality assessment							Summary of findings				Importance	
							No of patients		Effect			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute		
severe withdrawal symptoms (follow-up mean 1 weeks)												
3 ¹	randomized trials	no serious limitations	serious ²	no serious indirectness	no serious imprecision	none	9/56 (16.1%)	20/56 (35.7%)	RR 0.34 (0.14 to 0.85)	236 fewer per 1000 (from 54 fewer to 307 fewer)	MODERATE	CRITICAL
								10%		66 fewer per 1000 (from 15 fewer to 86 fewer)		
alcohol withdrawal seizures												
3 ³	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/149 (0.7%)	14/175 (8%)	RR 0.16 (0.04 to 0.69)	67 fewer per 1000 (from 25 fewer to 77 fewer)	HIGH	CRITICAL
								2%		17 fewer per 1000 (from 6 fewer to 19 fewer)		
								9%		76 fewer per 1000 (from 28 fewer to 86 fewer)		
death (follow-up 3 to 10 days)												
8 ⁴	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁵	none	0/250 (0%)	0/230 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW	CRITICAL
alcohol withdrawal delirium (follow-up mean 2 weeks)												
4 ⁶	randomized trials	serious ⁷	no serious inconsistency	no serious indirectness	serious ⁸	none	3/172 (1.7%)	11/186 (5.9%)	RR 0.31 (0.09 to 1.02)	41 fewer per 1000 (from 54 fewer to 1 more)	LOW	CRITICAL
failure to complete alcohol withdrawal (follow-up mean 2 weeks)												
3 ⁹	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹⁰	none	14/117 (12%)	26/156 (16.7%)	RR 0.69 (0.38 to 1.24)	52 fewer per 1000 (from 103 fewer to 40 more)	LOW	

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recurrent withdrawal seizures (within 6 hours) (follow-up 6 hours; observation)												
1 ¹¹	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹²	none	3/100 (3%)	21/86 (24.4%)	OR 0.10 (0.03 to 0.33)	213 fewer per 1000 (from 148 fewer to 235 fewer)	MODERATE	CRITICAL
recurrent withdrawal seizures (within 48 hours) (Copy) (follow-up 48 hours; ED records)												
1 ¹¹	randomized trials	serious ¹³	no serious inconsistency	no serious indirectness	serious ¹²	none	1/100 (1%)	7/86 (8.1%)	OR 0.11 (0.01 to 0.95)	72 fewer per 1000 (from 4 fewer to 81 fewer)	LOW	CRITICAL

¹ Ntais et al, 2005 review analysis 1.1 "therapeutic success" meaning prevention of severe withdrawal symptoms, but with outcomes reversed.

² I squared 52%.

³ Analysis 1.2. Kaim et al, 1969; Naranjo et al, 1983; Sellers et al, 1983.

⁴ All studies from Analysis 1.4 included.

⁵ No cases of death identified (250 Benzodiazepines, 230 Controls)

⁶ 4 papers identified by Mayo Smith, 1997 review (Kaim et al, 1969; Zilm et al, 1980; Sereny & Kalant 1965; Rosenfeld & Bizzoco, 1961). No papers identified by Ntais et al, 2005 review or Mayo-Smith et al, 2004 review.

⁷ One of 4 studies not randomly allocated (allocation rotated by presentation), Sereny & Kallant, 1965. Uncertain regarding Rosenfeld & Bizzoco, 1961 as unable to access paper.

⁸ Few cases reported: 3/172 BZD group, 11/186 in placebo group.

⁹ Ntais et al, 2005 analysis 1.3.

¹⁰ Small sample sizes. Small number of events. Wide confidence intervals.

¹¹ Study by D'Onofrio 1999 was the only study identified in the literature to examine this issue.

¹² Small sample sizes with small number of events.

¹³ Not all patients followed up. Relies on emergency department records for the city where 85% of patients lived.

Table 3

Author(s): N Lintzeris, N Clark

Date: 2009-08-04

Question: Should anticonvulsants (not sedating, i.e. not barbiturates or chlormethiazole) vs placebo be used for alcohol withdrawal?

Settings:

Bibliography: Polycarpou A et al (2005). Anticonvulsants for alcohol withdrawal. *Cochrane Database of Systematic Reviews*, (3):CD005064.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anticonvulsants (not sedating, i.e. not barbiturates or chlormethiazole)	placebo	Relative (95% CI)	Absolute		
withdrawal symptoms (at 48 hours) (follow-up 2 weeks)												
2 ¹	randomized trials	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	0/0 (0%)	0/0 (0%)	not pooled	not pooled	VERY LOW	IMPORTANT
alcohol withdrawal seizures (follow-up 7 days)												
3 ⁴	randomized trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/249 (1.2%)	20/240 (8.3%)	RR 0.2 (0.03 to 1.4)	67 fewer per 1000 (from 81 fewer to 33 more)	MODERATE	CRITICAL
completion of withdrawal (follow-up 7 days)												
2 ⁶	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	21/52 (40.4%)	21/49 (42.9%)	RR 0.99 (64 to 1.53)	4 fewer per 1000 (from 227 more to 27000)	LOW	IMPORTANT

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										more)		
Death												
5 ⁷	randomized trials	serious ⁸	no serious inconsistency	no serious indirectness	very serious ⁹	none	0/290 (0%)	0/287 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
prevention recurrent alcohol withdrawal seizures (follow-up 7 days)												
2 ¹⁰	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness ¹¹	serious ³	none	22/122 (18%)	23/123 (18.7%)	RR 0.96 (0.5 to 1.84)	7 fewer per 1000 (from 93 fewer to 157 more)	MODERATE	CRITICAL

¹ Analysis 1.1 and 1.2, Lambie et al, 1980 (valproate) and Bjorkqvist et al, 1976 (carbamazepine) included. Glatt et al, 1966 and Burroughs et al, 1985 examine chlormethiazole.

² Studies employed rescue medications (chlormethiazole).

³ Small sample size (wide confidence intervals).

⁴ Only Lambie et al, 1980 (valproate), Stanhope 1989 (carbamazepine), and Sampliner & Iber, 1974 (phenytoin) used appropriate interventions. Bonnet et al, 2003 used gabapentin. Some studies were post seizure (excluded).

⁵ Studies utilized rescue medications of tranquilisers/chlormethiazole for intolerable withdrawal symptoms. Stanhope used alternate rather than random allocation, double-blinded.

⁶ Bjorkqvist et al, 1976 and Reoux et al, 2001 from analysis 1.9 of Polycarpou et al, 2005

⁷ Analysis 1.10. Studies included: Bjorkqvist et al, 1976 (carbamazepine), Chance 1991 (phenytoin), Lambie et al, 1980 (valproate), Rathlev et al, 1994 (phenytoin), Stanhope 1989 (CBZ). Other studies examine chlormethiazole, gabapentin or other medications. Reoux et al, 2001 examined valproate + oxazepam v oxazepam.

⁸ Drop out rate of 53% in Bjorkqvist et al, 1976

⁹ No cases of death identified in 577 cases (155 followed up for only 6 hours post alcohol withdrawal seizure).

¹⁰ Analysis 1.5. Rathlev et al, 1994; Chance 1991. Both examine phenytoin.

¹¹ Both emergency department settings, as appropriate for condition (following alcohol withdrawal seizure).

Table 4

Author(s): N Clark, N Lintzeris

Date: 2009-08-05

Question: Should antipsychotics vs placebo be used for alcohol withdrawal?

Settings:

Bibliography: 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.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	neuroleptics	placebo	Relative (95% CI)	Absolute		
alcohol withdrawal seizures (follow-up 2-7 days)												
2 ¹	randomized trials	serious ²	no serious inconsistency ³	no serious indirectness	serious ⁴	none	14/121 (11.6%)	9/141 (6.4%)	RR 1.81 (0.82 to 4.01)	52 more per 1000 (from 11 fewer to 192 more)	LOW	CRITICAL
alcohol withdrawal delirium (follow-up 2-7 days)												

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2 ¹	randomized trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁶	none	8/121 (6.6%)	9/141 (6.4%)	RR 1.05 (0.42 to 2.62)	3 more per 1000 (from 37 fewer to 103 more)	LOW	CRITICAL
Death												
2 ¹	randomized trials	very serious ⁷	no serious inconsistency	no serious indirectness	very serious ⁸	none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	IMPORTANT

¹ Sereny & Kalant, 1965; Kaim et al, 1969.

² 1/2 studies not randomized (Sereny & Kalant, 1965).

³ Qualitative assessment.

⁴ Few cases identified: 14/121 intervention, 9/141 control group.

⁵ 1/2 studies not randomly allocated (Sereny & Kalant, 1965).

⁶ Few cases identified: 8/121 Phenothizines; 9/141 placebo.

⁷ Sereny & Kalant, 1965 not randomized.

⁸ No cases identified from 262 subjects.

Table 5

Author(s): N Lintzeris, N Clark

Date: 2009-08-05

Question: Should antipsychotics vs benzodiazepines be used for alcohol withdrawal?

Settings: inpatient

Bibliography: 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 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				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antipsychotics	benzodiazepines	Relative (95% CI)	Absolute		
alcohol withdrawal seizures												
3 ¹	randomized trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	19/155 (12.3%)	1/196 (0.5%)	RR 11.81 (2.78 to 50.09)	55 more per 1000 (from 9 more to 250 more)	LOW	CRITICAL
alcohol withdrawal delirium												
2 ⁴	randomized trials	serious ⁵	no serious inconsistency ⁶	no serious indirectness	serious ⁷	none	8/121 (6.6%)	1/151 (0.7%)	RR 5.94 (1.07 to 33.11)	33 more per 1000 (from 0 more to 213 more)	LOW	CRITICAL
								0%		0 more per 1000 (from 0 more to 0 more)		
								0.9%		44 more per 1000 (from 1 more to 289 more)		

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¹ Sereny & Kalant, 1965; Chambers & Schultz, 1965; Kaim et al, 1969. All examine phenothiazines.

² 1 / 3 studies not randomly allocated (Sereny & Kalant, 1965).

³ only 1 case identified in benzodiazepine group / 196 subjects; 19/ 155 in phenothiazine group.

⁴ Sereny & Kalant, 1965; Kaim et al, 1969. All examined phenothiazines.

⁵ 1/2 studies not randomly allocated (Sereny & Kalant, 1965).

⁶ Qualitative assessments.

⁷ Few cases: 1/154 in benzodiazepine group; 8/ 121 in phenothiazine group.

Additional information that was not GRADEd

Newer anticonvulsants were excluded because of their expense (i.e. gabapentin). Effective doses of benzodiazepines in the treatment of alcohol withdrawal can be fatal in patients not dependent on alcohol or other sedatives. Non sedating anticonvulsants probably have a safer safety profile and would be preferred if they had similar evidence of effectiveness. Doses of diazepam vary considerable and need to be tailored to the severity of withdrawal. This requires repeated patient observation, particularly in the inexperienced practitioner. Selecting the more severe cases of alcohol withdrawal for treatment with higher doses of benzodiazepines significantly reduces the risks of using benzodiazepines. All the studies were conducted in inpatient settings, although much alcohol withdrawal takes place in outpatient settings.

Reference List

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D'Onofrio et al (1999). Lorazepam for the prevention of recurrent seizures related to alcohol. *New England Journal of Medicine*, 340:915-9.

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Glatt MM, George HR, Frisch EP (1966). Evaluation of chlormethiazole in treatment for alcohol withdrawal syndrome. Results of a controlled trial. *Acta Psychiatrica Scandinavica Supplementum*, 192:121–37.

Kaim SC, Klett CJ, Rothfeld B (1969). Treatment of the acute alcohol withdrawal state: a comparison of four drugs. *American Journal of Psychiatry*, 125:54-60.

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Rathlev NK et al (1994). The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Annals of Emergency Medicine*, 23:513–8.

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From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	Benzodiazepines are safe and effective medications for the management of alcohol withdrawal, and are more effective than anticonvulsants and antipsychotic medications (phenothiazines) in preventing complications such as seizures and delirium, and in ameliorating the severity of alcohol withdrawal. Anticonvulsants (carbamazepine, phenytoin, valproate) are alternatives for those individuals who can not use benzodiazepines. The evidence appears stronger for the carbamazepine than phenytoin or valproate. Strongest evidence is for prevention of seizures, but they are not effective in preventing recurrent seizures in those who have already had one seizure. There is no evidence regarding their capacity to prevent delirium.

Management of alcohol withdrawal

	Antipsychotic medications (e.g. phenothiazines) are not recommended in managing alcohol withdrawal, and are not effective in preventing seizures or delirium compared to placebo. They are less effective than diazepam. Several studies found long acting benzodiazepines (e.g. diazepam, chlordiazepoxide) to be more effective than shorter-acting benzodiazepines, as there was an increase in withdrawal symptoms following the cessation of shorter-acting benzodiazepines. Few studies have examined different approaches to dose regimens with benzodiazepines - specifically whether dosing should be 'fixed' dosing schedules, or 'symptom triggered'. In residential settings with staff skilled in monitoring, symptom triggered regimes can be of benefit in reducing total medication requirements, however, they have limited role in outpatient settings, or for individuals with concomitant medical or psychiatric conditions. Barbituates and related sedatives (e.g. paraldehyde, chlormethiazole, chloral hydrate) are not recommended for alcohol withdrawal management due to safety concerns compared to safer medication approaches such as benzodiazepines.
Summary of the quality of evidence	Generally poor quality evidence, studies were generally underpowered and did not report all relevant outcomes. All studies were conducted in specialist residential settings.
Balance of benefits versus harms	Benzodiazepines clearly demonstrate evidence of benefits over harms. Antipsychotics clearly do not. Non sedating anticonvulsants demonstrate less advantages and probably also have less safety concerns so the balance is not clear.
Define the values and preferences including any variability and human rights issues	Alcohol abuse and dependence represents a most serious health problem worldwide with major social, interpersonal and legal interpolations. Dependence on alcohol is associated with both physiological symptoms such as tolerance and withdrawal, and behavioural symptoms such as impaired control over drinking.
Define the costs and resource use and any other relevant feasibility issues	Management of alcohol withdrawal can be resource intensive. In some cases, inpatient care might be required.

Final recommendation(s)

Supported withdrawal from alcohol should be advised in patients with alcohol dependence, as a precursor to treatment.

Strength of recommendation: STRONG

Benzodiazepines are recommended as front-line medication for the management of alcohol withdrawal in alleviating withdrawal discomfort, and preventing seizures and delirium. Long-acting benzodiazepines are recommended over shorter-acting ones, except in cases of impaired hepatic metabolism (e.g. liver failure, elderly). The dose and duration should be individually determined, according to the severity of withdrawal and the presence of other medical disorders. In general, the duration of benzodiazepines treatment should be limited to the first 3 to 7 days after the cessation of alcohol.

Strength of recommendation: STRONG

Antipsychotic medications should not be used as stand alone medications for the management of alcohol withdrawal.

Strength of recommendation: STRONG

Benzodiazepines, and not anticonvulsants, should be used following an alcohol withdrawal seizure for the prevention of further alcohol withdrawal seizures.

Strength of recommendation: STRONG

Psychoactive medication used for the treatment of alcohol withdrawal should be dispensed in small doses, or each dose supervised, to reduce the risk of misuse.

Strength of recommendation: STRONG

Patients at risk of severe withdrawal, or who have concurrent serious physical or psychiatric disorders, or who lack adequate support, should preferably be managed in an inpatient setting.

Strength of recommendation: STRONG

As part of withdrawal management, all patients should be given oral thiamine. Patients at high risk of Wernicke's Encephalopathy (malnourished, severe withdrawal) should be given 3 days parental thiamine.

Strength of recommendation: STRONG

In patients with suspected Wernicke's Encephalopathy, parenteral thiamine should be administered twice daily for 5 days.

Strength of recommendation: STRONG

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005063. DOI: 10.1002/14651858.CD005063.pub3. (**New search for studies and content updated (conclusions changed), published in Issue 3, 2010.**)

Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD008537. DOI: 10.1002/14651858.CD008537.pub2. (**New, published in Issue 6, 2011.**)

Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database of Systematic Reviews 2010, Issue 2. Art. No.: CD006266. DOI: 10.1002/14651858.CD006266.pub2. (**Edited (no change to conclusions), published in Issue 4, 2011.**)

Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005064. DOI: 10.1002/14651858.CD005064.pub3. (New search for studies and content updated (conclusions changed), published in Issue 3, 2010.)