

ALC 1: Baclofen for relapse prevention and management among people with alcohol dependence. [New 2015]

SCOPING QUESTION: In people with alcohol dependence post-detoxification, is baclofen effective for relapse prevention management of alcohol dependence?

BACKGROUND

Medications registered for the management of alcohol dependence include acamprosate, naltrexone and disulfiram; however, these medications are often not available in many settings and are also not effective for all patients. Baclofen is a Gamma-aminobutyric acid B (GABA-B) agonist that has been used extensively in the management of muscle spasms (including in chronic cases for patients with long-term spasticity) and in the treatment of epilepsy (Lyon et al., 2011). Extensive use for these indications has enabled a comprehensive evaluation of the adverse effect profile, which is regarded as acceptable (Garbutt et al., 2010). Although the treatment of alcohol dependence is not an approved indication, it is widely available and is commonly used “off label” in many countries, particularly in France, where regulatory authorities have issued a “Temporary Recommendation” for its use in the management of alcohol dependence (Lyon et al., 2011).

Baclofen is significantly more available and affordable than any of the medication currently recommended by WHO for the treatment of alcohol dependence. Its addition to WHO’s Essential Medicines List has significantly increased the availability of treatments for alcohol dependence. It is out of patent and available as a generic product, and is generally inexpensive. While baclofen is GABAergic, it is generally regarded to have a low abuse liability, although tolerance can occur and it can induce sedation. However, baclofen is considered less sedating than benzodiazepines (GABA-A agonists), and to have a milder withdrawal syndrome. Baclofen is regarded as safer in patients with alcohol induced liver disease than some other alternatives, which can be hepatotoxic. The aim of this scoping question is to update the recommendation with current available evidence and assess the extent to which baclofen still remains a relevant and effective choice for relapse prevention management of alcohol dependence.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with alcohol dependence, post-detoxification
- **Interventions:** Baclofen
- **Comparison:** Placebo
- **Outcomes:**
 - **Critical** – Alcohol use, abstinence
 - **Important** – Medication compliance, psychosocial function, adverse effects



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Search strategy

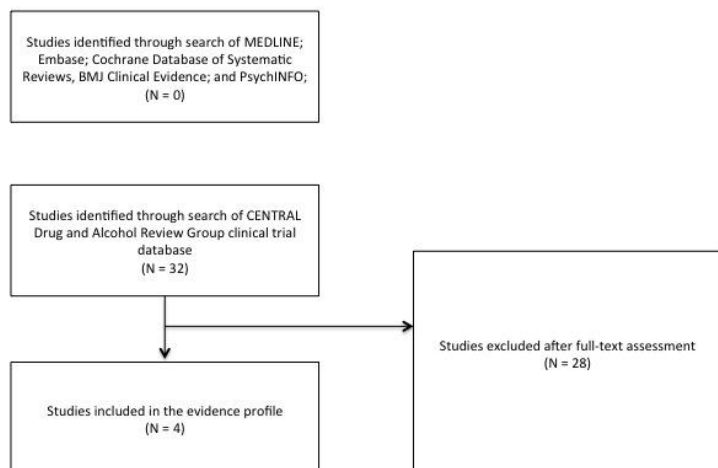
The studies of interest were randomized controlled trials (RCTs) comparing baclofen to either placebo or a lower dose of baclofen in the treatment of alcohol dependence.

To identify relevant systematic reviews, the following databases were searched: MEDLINE, Embase, The Cochrane Library, BMJ Clinical Evidence and PsychINFO up to September 2014, using the search strategy found in Appendix 1. No up-to-date systematic reviews were found.

To identify RCTs, the CENTRAL Drug and Alcohol Review Group clinical trial database was searched using the keywords “*baclofen AND (alcohol or alcoholism or alcoholic)*”, which revealed 32 abstracts.

The search for RCTs in CENTRAL identified 32 articles. These were screened for inclusion by a single researcher, which yielded four relevant studies. Figure 1 below outlines the search process and outcomes.

Figure 1. Search process and outcomes



Included in GRADE tables or footnotes

- Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedgoni G, Caputo F, Gasbarrini G, Landolfi R (2011). Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol and Alcoholism*.46(3):312-17.
- Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G (2007). Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*.370(9603):1915-1922.
- Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G (2002). Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol and Alcoholism*.37(5):504-8.
- Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA (2010). Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcoholism: Clinical and Experimental Research*.34(11):1849-1857.

Excluded from GRADE tables and footnotes

Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. *American Journal of Medicine*. 2006;119(3): 276.e13-8.

REASONS FOR EXCLUSION: Examines the use of baclofen in alcohol detoxification treatment.

Gache P and Hadengue A. Baclofen improves abstinence in alcoholic cirrhosis: still better to come? *Journal of Hepatology*. 2008;49(6):1083-5.

REASONS FOR EXCLUSION: Comprises a review of evidence and is not an RCT.

Krupitskiy EM, Burakov AM, Grinenko AIA, Borodkin IUS. [Effect of pharmacotherapy of affective disorders on the psycho-semantics of alcoholic patients].

Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinsko. 1995;95(6):67-71.

REASON FOR EXCLUSION: Does not include drug use outcomes.

Krupitskiy EM, Burakov AM, Ivanov VB, Karandashova GF, Lapin IP, Grinenko ALA, Borodkin IUS. [The use of baclofen for treating affective disorders in alcoholism].

Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinsko. 1994;94(1):57-61.

REASON FOR EXCLUSION: Does not include drug use outcomes.

Krupitskiy EM, Burakov AM, Ivanov VB, Karandashova GF, Lapin IP, Grinenko ALA, Borodkin IUS. Baclofen administration for the treatment of affective disorders in alcoholic patients. *Drug and Alcohol Dependence*. 1993;33(2):157-63.

REASON FOR EXCLUSION: Does not include drug use outcomes.

Leggio L, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM, Addolorato G (2012). Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. *Addictive Behaviors*.37(4):561-564.

REASON FOR EXCLUSION: Patients have comorbidities that make them prone to adverse effects.

PICO Table

Population: Adults with alcohol dependence					
Intervention	Comparison	Outcome	Study used for GRADE	Justification for RCT used	Relevant GRADE Table
Baclofen (30-60 mg/day)	Placebo	Abstinence, medication compliance	Addolorato et al. (2007) Addolorato et al. (2011) Garbutt et al. (2010)	Recent RCTs which fitted inclusion/exclusion criteria	Table 1
		Psychosocial function, adverse effects	No data	No data	No data
High dose baclofen (60mg/day)	Low dose baclofen (20mg/day)	Abstinence, drinks per day, medication compliance	Addolorato et al. (2011)	Recent RCT which fitted inclusion/exclusion criteria	Table 2
Baclofen pre-detoxification	Placebo	Abstinence	Addolorato et al. (2002)	Recent RCT which fitted inclusion/exclusion criteria	Table 3
		Psychosocial function, adverse effects	No data	No data	No data

Narrative description of the studies that went into the analysis

Addolorato et al. (2011) explored the effect of baclofen in a dose of 20 mg three times per day, compared with 10 mg three times per day, in the treatment of alcohol dependence. The authors present a secondary analysis of a 12-week double-blind, placebo-controlled, randomized clinical trial with two doses of baclofen, specifically 10 mg t.i.d. and 20 mg t.i.d. There were 94 subjects consecutively screened post-detoxification from an alcohol treatment ward, with 42 subjects randomized into the study. Fourteen of the 42 patients were randomly allocated to placebo; 14 to the group treated with baclofen 10 mg t.i.d.; and 14 to the group treated with baclofen 20 mg t.i.d. Compared with patients allocated to placebo, patients allocated to the 10mg group had a 53% reduction in the number of drinks per day ($P < 0.0001$) and patients allocated to the 20mg group had a 68% reduction in the number of drinks per day ($P < 0.0001$), with respect to the number of



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drinks per day during the 28 days before randomization. The effect of baclofen 20mg t.i.d. was greater than that of baclofen 10 mg t.i.d. ($P = 0.0214$, Wald test), showing a dose-effect relationship. Both doses of baclofen were well tolerated.

Addolorato et al. (2007) investigated the effectiveness and safety of baclofen in achieving and maintaining alcohol abstinence in patients with liver cirrhosis. 148 alcohol-dependent patients with liver cirrhosis were referred to the Institute of Internal Medicine in Rome, Italy between October, 2003 and November, 2006. There were 84 subjects who were randomly allocated either oral baclofen or placebo for 12 weeks. The primary outcome was the proportion of patients achieving and maintaining alcohol abstinence. Measures of this outcome were total alcohol abstinence and cumulative abstinence duration, which were assessed at outpatient visits. Relapse was defined as alcohol intake of more than four drinks per day or overall consumption of 14 or more drinks per week over a period of at least four weeks. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number [NCT00525252](https://clinicaltrials.gov/ct2/show/study/NCT00525252). Of the 42 patients allocated baclofen, 30 (71%) achieved and maintained abstinence compared with 12 (29%) of 42 who were assigned placebo (odds ratio 6.3 [95% CI 2.4-16.1]; $p=0.0001$). The number of dropouts (termination of treatment) did not differ between the baclofen (6/42 [14%]) and placebo (13/42 [31%]) groups ($p=0.12$). Cumulative abstinence duration was about twofold higher in patients allocated baclofen than in those assigned placebo (mean 62.8 [SE 5.4] vs 30.8 [5.5] days; $p=0.001$). No hepatic side-effects were recorded.

Garbutt et al. (2010) tested the efficacy and tolerability of baclofen in alcohol dependence in the United States. The study was a double-blind, placebo-controlled, randomized study comparing 30 mg per day of baclofen to placebo over 12 weeks of treatment and utilizing eight sessions of BRENDA, a low-intensity psychosocial intervention. There were 121 subjects screened to yield 80 randomized subjects (44 men) with randomization balanced for gender. Percent of heavy drinking days was the primary outcome measure, with other drinking outcomes, anxiety levels and craving as secondary outcomes. Tolerability was examined. The study completion rate was 76%. No difference by drug condition was seen in terms of percentage of heavy drinking days where on-average rates were 25.5% ($\pm 23.6\%$) for placebo and 25.9% ($\pm 23.2\%$) for baclofen during treatment ($t(73)=0.59$, $p=0.56$). Similarly, no differences were seen by drug condition in percentage of days abstinent, time to first drink or time to relapse to heavy drinking. Baclofen was associated with a significant reduction in state anxiety ($F(1,73)= 5.39$, $p=0.02$). Baclofen was well tolerated with only two individuals stopping baclofen because of adverse events. There were no serious adverse events.

Addolorato et al. (2002) conducted a double-blind placebo-controlled design to provide a first evaluation of the efficacy of baclofen in inducing and maintaining abstinence and reducing craving for alcohol in alcohol-dependent patients. A total of 39 alcohol-dependent patients were consecutively enrolled in the study. After 12-24 hours of abstinence from alcohol, patients were randomly divided into two groups. There were 20 patients treated with baclofen and 19 with placebo. The medication and placebo were orally administered for 30 consecutive days. Baclofen was administered at the dose of 15mg per day for the first 3 days and 30mg per day for the subsequent 27 days, divided into three daily doses. Patients were monitored as out-patients on a weekly basis. At each visit alcohol intake, abstinence from alcohol, alcohol craving and changes in affective disorders were evaluated. A higher percentage of subjects totally abstinent from alcohol and a higher number of cumulative abstinence days throughout the study period were found in the baclofen, compared to the placebo, group. A decrease in the obsessive and compulsive components of craving was found in the baclofen compared to the placebo group; furthermore, alcohol intake was reduced in the baclofen group. A decrease in state anxiety was found in the baclofen compared to the placebo group. No significant difference was found between the two groups in terms of current depressive symptoms. Baclofen proved to be easily manageable and no patient discontinued treatment due to the presence of side-effects. No patient was affected by craving for the drug and/or drug abuse.

GRADE Tables

Table 1. Baclofen 5-10 mg t.i.d.ⁱ vs. placebo for relapse prevention management of alcohol dependence post-detoxification

Authors: N Clark and L Amato

Question: In adults with alcohol dependence, is baclofen 5-10 mg t.i.d. effective for relapse prevention management of alcohol dependence post-detoxification compared to placebo?

Bibliography:

1. Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedgoni G, Caputo F, Gasbarrini G, Landolfi R (2011). Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol and Alcoholism*.46(3):312-17.
2. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G (2007). Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*.370(9603):1915-1922.
3. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA (2010). Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcoholism: Clinical and Experimental Research*.34(11):1849-1857.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen (5-10mg t.i.d.)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
3	Randomized trials	Serious ²	Not serious	Not serious	Serious ³		42/96 (43.8%)	18/96 (18.8%)	OR 4.91 (2.29 to 10.52)	344 more per 1000 (from 158 more to 521 more)	⊕⊕○○ LOW	CRITICAL
								28.57%		377 more per 1000 (from 192 more to 522 more)		
Medication compliance												
3	Randomized trials	Not serious	Serious ¹	Not serious	Serious ¹		76/96 (79.2%)	69/96 (71.9%)	OR 1.47 (0.76 to	71 more per 1000	⊕⊕○○	IMPORTANT



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Quality assessment							No, of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen (5-10mg t.i.d.)	Placebo	Relative (95% CI)	Absolute (95% CI)		
									2.83)	(from 59 fewer to 160 more)	LOW	
								69.05%		76 more per 1000 (from 61 fewer to 173 more)		
Psychosocial function												
Adverse effects												

1. Significant heterogeneity.
2. Open label studies.
3. Small number of events and small number of participants.

Figure 2. Forest plot of comparison: Baclofen post-detoxification vs. placebo – abstinence at 12 weeks

Baclofen for Alcohol dependence

05-Dec-2014

1 Baclofen (5–10mg tid) vs placebo for relapse prevention post detox

1.1 Abstinence

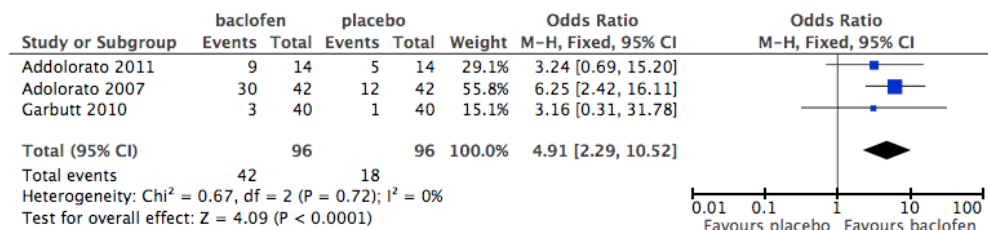


Figure 3. Forest plot of comparison: Baclofen post-detoxification vs. placebo – medication compliance

Baclofen for Alcohol dependence

05-Dec-2014

1 Baclofen (5–10mg tid) vs placebo for relapse prevention post detox

1.2 Medication compliance

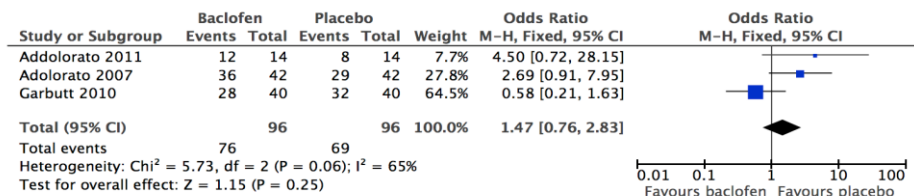


Table 2. Baclofen 60 mg/day vs. baclofen 20 mg/day for relapse prevention management of alcohol dependence

Authors: Clark N, Amato L

Question: In adults with alcohol dependence, is baclofen 60 mg/day effective for relapse prevention management of alcohol dependence post-detoxification compared to baclofen 20 mg/day?

Bibliography (systematic reviews): Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedgoni G, Caputo F, Gasbarrini G, Landolfi R (2011). Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. Alcohol and Alcoholism.46(3):312-17.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen 60 mg/day	Baclofen 20 mg/day	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
1	Randomized trials	Serious ¹	Not serious	Not serious	Very serious ³		11/14 (78.6%)	9/14 (64.3%)	OR 2.04 (0.38 to 10.94)	143 more per 1000 (from 237 fewer to 309 more)	⊕○○○ VERY LOW	CRITICAL
								64.29%		143 more per 1000 (from 237 fewer to 309 more)		
Medication compliance												
1	Randomized trials	Serious ¹²	Not serious	Not serious	Very serious ³		12/14 (85.7%)	12/14 (85.7%)	OR 1 (0.12 to 8.31)	0 fewer per 1000 (from 123 more to 439 fewer)	⊕○○○ VERY LOW	IMPORTANT
								85.71%		0 fewer per 1000 (from 123 more to 439 fewer)		
Alcohol use – Drinks per day												
1	Randomized trials	Serious ¹²	Not serious	Not serious	Serious ⁴		14	14	-	MD 0.35 lower (0.63 lower to 0.07 lower)	⊕⊕○○ LOW	CRITICAL

1. Unblinded.
2. Open label.
3. Very wide confidence interval.
4. Small number of participants.

Table 3. Baclofen vs. placebo for relapse prevention management of alcohol dependence pre-detoxification.

Authors: N Clark and L Amato

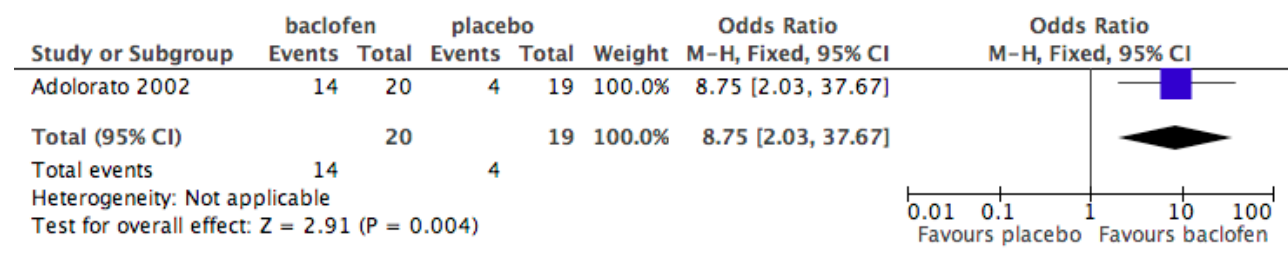
Question: In adults with alcohol dependence, is baclofen effective for relapse prevention management of alcohol dependence pre-detoxification compared to placebo?

Bibliography (systematic reviews): Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G (2002). Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol and Alcoholism.37(5):504-8.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo pre-detoxification	Relative (95% CI)	Absolute (95% CI)		
Abstinence												
1	Randomized trials	Serious 2	Not serious	Serious 1	Very serious 3	Very strong association	14/20 (70.0%)	4/19 (21.1%)	OR 8.75 (2.03 to 37.67)	489 more per 1000 (from 141 more to 699 more)	⊕⊕⊕⊕ LOW	CRITICAL
								21.1%		489 more per 1000 (from 141 more to 699 more)		
Medication compliance												
1	Randomized trials	Serious 2	Not serious	Serious 1	Serious 3	Strong association	17/20 (85.0%)	11/20 (55.0%)	OR 4.64 (1.02 to 21.00)	300 more per 1000 (from 5 more to 413 more)	⊕⊕⊕⊕ LOW	IMPORTANT
								55.0%		300 more per 1000 (from 5 more to 413 more)		

1. Pre-detoxification population is indirectly related to the target population.
2. Blinding not likely to have been effective, given the psychoactive effects of baclofen.
3. Small study (n=40) with wide confidence intervals.

Figure 3. Forest plot of comparison: Baclofen pre-detoxification vs. placebo – abstinence at 12 weeks



PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Outcome	Intervention (Number of studies, Odds Ratio [95% CI], Quality of evidence)		
	Baclofen 5-10 mg t.i.d.	Baclofen 20mg t.i.d. (60 mg/day)	Baclofen pre-detox
Abstinence	3 studies OR 4.91 (2.29 to 10.52) Favours baclofen LOW quality	1 study OR 2.04 (0.38 to 10.94) No difference VERY LOW quality	1 study OR 8.75 (2.03 to 37.67) Favours baclofen LOW quality
Alcohol use	No data	1 study MD /0.35 (0.63 lower to 0.07 lower) Favours baclofen LOW quality	No data
Medication compliance	3 studies OR 1.47 (0.76 to 2.83) No difference LOW quality	1 study OR 1 (0.12 to 8.31) No difference LOW quality	1 study OR 4.64 (1.02 to 21.00) Favours baclofen LOW quality
Psychosocial function	No data	No data	No data
Adverse effects	No data	No data	No data

Evidence to recommendation

Benefits	There is short-term evidence suggesting that baclofen improves abstinence from alcohol compared to placebo.
Harms	There was no increase in medication cessation with baclofen compared to placebo. There were no serious side effects reported; however, baclofen can cause sedation and cessation of baclofen can be associated with a mild benzodiazepine-like withdrawal syndrome that requires gradual cessation.
Summary of the quality of evidence	The search for RCTs identified 18 articles, 4 of which met the inclusion criteria for this review. Quality of evidence varies between LOW and MODERATE . There are no data in the long term.

Value and preferences

In favour	Patients value affordable and available treatments for alcohol dependence.
Against	The lack of formal approval for baclofen's use for alcohol dependence places increased responsibility on the medical practitioner prescribing baclofen to inform patients of the risks and benefits of its use for alcohol dependence.
Uncertainty or variability?	There is variability in the value of baclofen. The medication is mildly sedating, which is valued by many patients with alcohol dependence and not valued by others.

Feasibility (including resource use considerations)	Treatment is feasible in low-resource and primary-care settings. Baclofen is a generic product and is inexpensive and generally widely available.
Uncertainty or variability?	There is both variability and uncertainty in the feasibility of baclofen for relapse prevention of alcohol dependence. Baclofen is not available in all countries and is not registered for the use of alcohol dependence.

Recommendation and remarks

Recommendation

Baclofen can be offered to prevent relapse among people with alcohol dependence post-detoxification.

Rationale: There is short-term evidence suggesting that baclofen improves abstinence from alcohol compared to placebo. There were no serious side effects reported; however, baclofen can cause sedation and cessation of baclofen can be associated with a mild benzodiazepine-like withdrawal syndrome. Patients value affordable and available treatments for alcohol dependence. Baclofen is available in generic form and is inexpensive. Baclofen may not be available in all countries and is not registered for the use of alcohol dependence.

Remarks

A dose of 10mg three times a day is recommended initially, but can be increased to 20mg three times a day if needed.

Baclofen should be reduced gradually rather than stopped abruptly because of the risk of a mild benzodiazepine withdrawal-like syndrome.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low
Balance of benefits versus harms	<input checked="" type="checkbox"/> Benefits clearly outweigh harms <input type="checkbox"/> Benefits and harms are balanced <input type="checkbox"/> Potential harms clearly outweigh potential benefits
Values and preferences	<input checked="" type="checkbox"/> No major variability <input type="checkbox"/> Major variability
Resource use	<input checked="" type="checkbox"/> Less resource-intensive <input type="checkbox"/> More resource-intensive
Strength	CONDITIONAL



[New 2015]

OTHER REFERENCES

Lyon JE, Khan RA, Gessert CE, Larson PM, Renier CM (2011). Treating alcohol withdrawal with oral baclofen: a randomized, double-blind, placebo-controlled trial. *Journal of Hospital Medicine*.6:469-74.

Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA (2010). Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcoholism, Clinical and Experimental Research*.34(7):1849-57.

ⁱ "ter in die" or three times a day (t.i.d.)