Q4: Are acamprosate, disulfiram and naltrexone safe and effective in preventing relapse in alcohol dependence in non-specialized health care settings?

Background

Treatment for alcohol dependence may usually be considered to have two distinct but interrelated arms. Firstly, it is helping the individual to stop or reduce alcohol use. The second arm is prevention of relapse. The two arms, although distinct processes, have an important relationship in terms of timing (Prochaska et al, 1992). Prevention of relapse may involve psychosocial (a combination of psychological and social) and pharmacological interventions. Pharmacological interventions used in alcohol dependence for prevention of relapse include acamprosate, disulfiram and naltrexone. It is not clear which of them should be used.

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

Population:	alcohol dependence
Interventions:	acamprosate
	naltrexone
	disulfiram
Comparison:	placebo
	one medication vs other
Outcomes:	proportion relapsed to heavy alcohol drinking
	alcohol consumption: proportion abstinent and proportion drinking days
	alcohol related health outcomes (including psychosocial functioning)

adverse events

mortality

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Rosner S et al (2008). Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *Psychopharmacology,* 22:11-23.

Boothby LA, Doering PL (2005). Acamprosate for the treatment of alcohol dependence. *Clinical Therapeutics,* 27:695-714. . Included as identified acamprosate v placebo studies with quality of life outcome data.

Srisurapanont M, Jarusuraisin N (2005). Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*, (1):CD001867. Included as identified naltrexone v placebo studies with health outcome data.

EXCLUDED FROM GRADE TABLES AND FOOTNOTES

The following meta-analyses were not used as less comprehensive data from individual studies compared to Rosner et al, 2008 who contacted researchers for data not reported in original papers: Mann et al, 2004; Boothby et al, 2005; Srisurapanont & Jarusuraisin 2005.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Naltrexone vs. placebo	Proportion relapsed to heavy alcohol drinking Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial	Rosner et al, 2008	Best up to date review with added data from authors

		functioning) Adverse events Mortality		
2	Acamprosate vs. placebo	Proportion relapsed to heavy alcohol drinking Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial functioning) Adverse events Mortality	Rosner et al, 2008	Best up to date review
3	Disulfiram vs. placebo	Proportion relapsed to heavy alcohol drinking Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial functioning) Adverse events Mortality	New review carried out as part of this evidence profile	No adequate review available including recent studies
4	Naltrexone vs. acamprosate	Proportion relapsed to heavy alcohol drinking Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial functioning) Adverse events Mortality	New review carried out as part of this evidence profile	No adequate review available including recent studies.
5	Naltrexone vs. disulfiram	Proportion relapsed to heavy alcohol drinking	New review carried out as part of this evidence profile	No adequate review available including recent studies

		Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial functioning) Adverse events Mortality		
6	Acamprosate vs. disulfiram	Proportion relapsed to heavy alcohol drinking Alcohol consumption: proportion abstinent and proportion drinking days Alcohol related health outcomes (including psychosocial functioning) Adverse events Mortality	New review carried out as part of this evidence profile	No adequate review available including recent studies.

Narrative description of the studies that went into the analysis

Rosner et al, 2008 included 21 RCTs of acamprosate compared to placebo, with 5280 subjects. The studies were European, except for 1 each conducted in Brazil, Korea and USA. Study sample sizes ranged from n=26 (Niederhofer & Staffen, 2003) to n=581 (Chick et al, 2000). Acamprosate treatment was usually initiated several days after stopping alcohol (accommodating a withdrawal period), and study duration varied from 2 months to 1 year, with most studies lasting 6 months.

Rosner et al. 2008 reviewed 20 RCTs of naltrexone compared to placebo, studying 2182 subjects. Most were conducted in USA (n=11) and Europe (n=6), with 2 in Australia and one in Asia. Most studies were 90 day duration (ranging from 51 days (Latt et al, 2002) to 1 year (Krystal et al, 2001), with study sample sizes from n=44 (Oslin et al, 1997) to n=360 (Krystal et al, 2001). Naltrexone was generally initiated immediately following a period for alcohol withdrawal.

The review of disulfiram vs. placebo and the comparative reviews between medications were original meta-analyses conducted by the review team. Studies were identified using Pubmed Clinical Query and hand searches of related published papers.

Preventing relapse in alcohol dependent patients

- Five RCTs were identified comparing disulfiram to placebo (Fuller & Roth, 1979; Fuller et al, 1986; Niederhofer & Staffen, 2003; Petrakis et al, 2005; Chick et al, 1992), with 735 subjects. Three studies were conducted in the USA and two in Europe.
- Five RCTs were identified comparing naltrexone with acamprosate (Morley et al,2006; Kiefer et al,2003; Rubio et al, 2001; Laaksonen et al, 2008; Anton et al,2006) with 1119 subjects - 3 in Europe, I in USA and 1 in Australia.
- Three studies comparing naltrexone with disulfiram (Petrakis et al, 2005; Laaksonen et al, 2008; DeSousa 2004), n = 387, and two studies comparing acamprosate with disulfiram (Laaksonen et al, 2008; DeSousa 2005) (n= 262) were identified. One further randomized study comparing naltrexone, acamprosate and disulfiram was identified (von Bardeleben et al, 1999), but data was not presented on an intention to treat, and only median values were reported, such that the data was not included in the meta-analyses. Studies incorporating disulfiram have tended to be open-label, due to the safety concerns of patients using alcohol whilst taking disulfiram. Consequently blinding of disulfiram studies was inadequate, compared to studies of other medications that were generally double blinded.

Subjects in the studies were alcohol dependent patients, generally without severe psychiatric or physical co-morbidity, or dependence to other drugs. There were several exceptions. Rosner et al. 2008 included one study, Hersh et al, 1998 that used naltrexone for the treatment of patients with cocaine and alcohol dependence. Petrakis et al, 2005 recruited subjects with alcohol dependence and active Axis I depression or anxiety disorder.

Another factor to consider is the considerable diversity in the extent to which psychosocial interventions accompanied pharmacotherapies. Most studies included intensive psychosocial components (e.g. Cognitive behavioural therapy (CBT) programs, group programs), detracting from the ability to generalize to less intensive treatment settings. Nevertheless, some studies (e.g. COMBINE project reported in Anton et al, 2005) suggest that the addition of structured cognitive behavioural interventions to medication groups (naltrexone, acamprosate) did not significantly improve outcomes compared to groups receiving medication and standard medical care without cognitive behavioural interventions. Other recent studies (DeSousa 2004; DeSousa 2005) have also examined the role of these medications with less structured psychosocial interventions, or employed psychosocial interventions that could be delivered by medical practitioners (Laaksonen et al, 2008).

Several recent studies examining naltrexone and acamprosate (Anton et al, 2006, Morley 2006) have been published since the Rosner et al, 2008 review and are not included in the analyses of naltrexone vs placebo and acamprosate vs placebo. Both studies found acamprosate to have no significant benefits over placebo on a range of drinking outcomes, whilst Anton et al, 2006 but not Morley et al, 2006 showed that naltrexone had superior outcomes to placebo. Two studies have examined combination pharmacotherapies - Anton et al, 2006 examined combination naltrexone and acamprosate, whilst Petrakis et al, 2005 examined combination naltrexone and disulfiram. Neither study found any advantages over mono-drug therapy.

GRADE tables

Table 1

Author(s): N Lintzeris, N Clark
Date: 2009-08-05
Question: Should naltrexone vs. placebo be used for alcohol dependence?
Settings: Outpatient
Bibliography: Rosner S et al (2008). Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *Psychopharmacology,* 22:11-23.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	naltrexone	placebo	Relative (95% CI)	Absolute		
Relapsed (follow-up median 12 weeks[1])												
19	randomized trials	no serious limitations	serious[2]	serious[3]	no serious imprecision	reporting bias	568/1213 (46.8%)	678/1198 (56.6%)	RR 0.80 (0.71 to 0.91)[4]	113 fewer per 1000 (from 51 fewer to 164 fewer)	VERY LOW	CRITICAL
								30%		60 fewer per 1000 (from 27 fewer to 87 fewer)		
								90%		180 fewer per 1000 (from 81 fewer to 261 fewer)		
Drinkers (follow-up 12-52 weeks[5])												
18[6]	randomized trials	no serious limitations	no serious inconsistency[7]	serious[8]	no serious imprecision	reporting bias[9]	740/1106 (66.9%)	799/1097 (72.8%)	RR 0.93 (0.88 to 0.99)[10]	51 fewer per 1000 (from 7 fewer to 87 fewer)	LOW	IMPORTANT
								50%		35 fewer per 1000 (from 5 fewer to 60 fewer)		
								90%		63 fewer per 1000 (from 9 fewer to 108 fewer)		
Proportion drinking days (follow-up 12-52 weeks[11]; measured with: drinking days per week; Better indicated by lower values)												
5	randomized trials	no serious limitations	serious[12]	serious[13]	no serious imprecision	reporting bias[14]	630	629[15]	-	SMD 0.14 lower (0 higher to 0.03 lower)	VERY LOW	IMPORTANT

[1] Range from 51 days to 12 months. Most studies 12 weeks.
[2] I squared = 64.6%.
[3] Almost all studies had intensive psychosocial interventions. Conducted in specialist addiction settings.
[4] MH, random effects model.
[5] Most studies 12 week outcomes.
[6] All studies from Figure 2, Rosner et al, 2008.

[7] I squared = 33.8%.
[8] No explanation was provided.
[9] Funnel plot indicates publication bias. Studies >2005 not included (including Anton et al, 2006; Morley et al, 2006) which demonstrate minor effects of naltrexone.
[10] MH, fixed-effects model.
[11] Most studies short duration (12 weeks).
[12] Data not presented in review. Conservative estimate of I squared > 50%.
[13] Studies included intensive psychosocial services, conducted in specialist addiction settings.
[14] Funnel plot indicates publication bias. Studies >2005 not included (including Anton et al, 2006; Morley et al, 2006) which demonstrate minor effects of acamprosate.
[15] Precise numbers not provided. Total numbers in studies = 1259. Estimated that half in naltrexone groups (consistent with pool of naltrexone studies).

Table 2

Author(s): N Lintzeris, N Clark
Date: 2009-08-11
Question: Should acamprosate vs. placebo be used for alcohol dependence?
Settings: Outpatients
Bibliography: Rosner S et al (2008). Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *Psychopharmacology,* 22:11-23.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acamprosate	placebo	Relative (95% CI)	Absolute		
Drinkers (follow-up 2-12 months[1])												
20	randomized trials[2]	no serious limitations	very serious[3]	serious[4]	no serious imprecision	reporting bias[5]	1833/2507 (73.1%)	1877/2270 (82.7%)	RR 0.84 (0.78 to 0.91)[6]	132 fewer per 1000 (from 74 fewer to 182 fewer)	VERY LOW	IMPORTANT
								50%		80 fewer per 1000 (from 45 fewer to 110 fewer)		
								90%		144 fewer per 1000 (from 81 fewer to 198 fewer)		
Relapsed (follow-up 2-12 months[7])												
11	randomized trials	no serious limitations	very serious[8]	serious[9]	no serious imprecision	reporting bias[10]	908/1615 (56.2%)	1029/1557 (66.1%)	RR 0.82 (0.73 to 0.92)	119 fewer per 1000 (from 53 fewer to 178 fewer)	VERY LOW	CRITICAL
								30%		54 fewer per 1000 (from 24 fewer to 81 fewer)		
								90%		162 fewer per 1000 (from 72 fewer to 243 fewer)		
Proportion drinking days (follow-up 2-12 months[11]; measured with: drinking days per week ; range of scores: -7-+7; Better indicated by lower values)												
14	randomized trials	no serious limitations	serious[12]	serious[13]	no serious imprecision	reporting bias[14]	1933[15]	1933[16]	-	SMD 0.19 lower (0.26 to 0.13 lower)[17]	VERY LOW	IMPORTANT

[1] Most studies of 6 months duration.
[2] all studies in Fig 1, Rosner et al, 2008 included.
[3] I squared = 83.6%.
[4] Most studies had intensive psychosocial interventions, conducted in specialist addiction settings.
[5] Funnel plot indicates publication bias. Studies >2005 not included (inc Anton 2006, Morley 2006) which demonstrate minor effects of acamprosate.
[6] MH, random effects.
[7] Most studies 6 months duration.
[8] I squared = 75.5%.
[9] Most studies included intensive psychosocial supports, and conducted in specialist settings. One study in Korea, one in Brazil, remainder in Europe-USA.
[10] Studies since 2005 not included (e.g. Anton et al, 2005; Morley et al, 2006).
[11] Most studies 6 months.
[12] Not stated in review. Conservative estimate of I squared >50%.
[13] Most studies included intensive psychosocial supports, and conducted in specialist settings.
[14] Studies since 2005 not included (e.g. Anton et al, 2005, Morley et al, 2006).
[15] Precise numbers not provided. Total numbers in studies = 3866. Estimated that half in acamprosate groups (consistent with pool of acamprosate studies).
[16] Precise numbers not provided. Total numbers in studies = 3866. Estimated that half in acamprosate groups (consistent with pool of acamprosate studies).
[17] An SMD of <0.4 is a small effect size according to Cohen's interpretation of effect size.

Table 3

Author(s): Lintzeris N & Clark N
Date: 2009-08-14
Question: Should disulfiram vs. placebo or no treatment be used for alcohol dependence?
Settings:
Bibliography: Lintzeris N, Clark N, Wong J. Disulfiram versus placebo for alcohol dependence.(in press).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	disulfiram	placebo or no treatment	Relative (95% CI)	Absolute		
abstinence (follow-up 3-12 months; self report or independent assemment)												
4[1]	randomized trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	105/324 (32.4%)	81/315 (25.7%)	RR 1.22 (1 to 1.49)	57 more per 1000 (from 0 more to 126 more)	LOW	CRITICAL
								15.7%		35 more per 1000 (from 0 more to 77 more)		
Proportion of abstinent days (%) (follow-up 3-6 months; Better indicated by higher values)												

2[4]	randomized trials	very serious[5]	serious[6]	serious[7]	no serious imprecision	none	60	59	-	MD 28 higher (2.74 to 53.26 higher)	VERY LOW	CRITICAL
alcohol consumption (change from baseline) (follow-up mean 6 months; Better indicated by lower values)												
1[8]	randomized trials	no serious limitations	no serious inconsistency	serious[9]	serious[10,11]	none	63	59	-	MD 57 lower (0.12 to 113.88 lower)		IMPORTANT
psychosocial functioning (follow-up 12 months; clinician assessment of good psychosocial function)												
1[12]	randomized trials	no serious limitations	no serious inconsistency	serious[9]	serious[11]	none	149/202 (73.8%)	134/199 (67.3%)	RR 1.36 (0.89 to 2.1)	242 more per 1000 (from 74 fewer to 741 more)	LOW	CRITICAL
								0%		0 more per 1000 (from 0 fewer to 0 more)		
health outcomes												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
adverse effects (follow-up 3-12 months; severe adverse events)												
4[13]	randomized trials	serious[2]	no serious inconsistency	serious[9]	serious[11]	none	12/344 (3.5%)	6/335 (1.8%)	RR 1.99 (0.74 to 5.38)	18 more per 1000 (from 5 fewer to 78 more)		IMPORTANT
								0%		0 more per 1000 (from 0 fewer to 0 more)		
mortality (follow-up mean 3-12 months)												
4[13]	randomized trials	serious[2]	no serious inconsistency	serious[9]	serious[11]	none	0/344 (0%)	1/335 (0.3%)	RR 0.32 (0.01 to 7.96)	2 fewer per 1000 (from 3 fewer to 21 more)	VERY LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		

[1] Fuller & Roth, 1979; Fuller et al, 1986; Niederhofer & Staffen, 2003; Petrakis et al, 2005; Chick et al, 1992.

[2] Loss to follow up greater than 30% in one study.

[3] Studies in specialist settings - 1 in adolescents (aged 16-19) (Niederhofer & Staffen, 2003), 1 psychiatric co-morbidity (Petrakis et al, 2005)

[4] Niederhofer & Staffen, 2003; Chick et al, 1992.

[5] 1 out of 2 studies with drop out rates greater than 30%.
[6] I squared = 66%.
[7] Studies in specialist settings - 1 in adolescents (aged 16-19) (Niederhofer & Staffen, 2003), 1 psychiatric co-morbidity (Petrakis et al, 2005).
[8] Chick et al, 1992.
[9] The study was conducted in alcoholism treatment centres.
[10] No explanation was provided.
[11] Wide confidence intervals.
[12] Fuller et al, 1986.
[13] Fuller et al, 1986; Chick et al, 1992; Niederhofer & Staffen; 2003, Petrakis et al, 2005.

Table 4

Author(s): N Lintzeris, N Clark
Date: 2009-08-10
Question: Should naltrexone vs. acamprosate be used for alcohol dependence?
Settings: Outpatient
Bibliography: Lintzeris N, Clark N. Naltrexone versus acamprosate for alcohol dependence (in press).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	naltrexone	acamprosate	Relative (95% CI)	Absolute		
% Abstinent (follow-up 12-52 weeks[1]; self-report)												
4[2]	randomized trials	no serious limitations	serious[3]	serious[4]	no serious imprecision	None	95/251 (37.8%)	74/256 (28.9%)	RR 1.28 (0.87 to 1.9)[5]	81 more per 1000 (from 38 fewer to 260 more)	LOW	IMPORTANT
								26.3%		74 more per 1000 (from 34 fewer to 237 more)		
% Relapsed												
5[6]	randomized trials	no serious limitations	serious[7]	serious[8]	no serious imprecision	None	345/560 (61.6%)	334/559 (59.7%)	RR 1.03 (0.88 to 1.2)	18 more per 1000 (from 72 fewer to 119 more)	LOW	CRITICAL
								65.4%		20 more per 1000 (from 78 fewer to 131 more)		
Time to first drink (days) (follow-up 12-52 weeks[9]; measured with: days; Better indicated by higher values)												
3[10]	randomized trials	no serious limitations	serious[11]	serious[12]	no serious imprecision	None	211	216	-	MD 4.18 higher (0.45 lower to 8.8 higher)	LOW	IMPORTANT
Time to first relapse (days) (Better indicated by higher values)												
3[13]	randomized trials	no serious limitations	very serious[14]	serious[15]	no serious imprecision	None	211	216	-	MD 4.79 higher (0.24 lower to 9.83 higher)	VERY LOW	IMPORTANT
Proportion abstinent days (%) (Better indicated by higher values)												
4[16]	randomized	no serious	serious[17]	serious[18]	no serious	None	520	519	-	MD 2.2 higher (4.38 lower to		IMPORTANT

	trials	limitations			imprecision					8.78 higher)	LOW	
Good clinical outcome (mild dependence/GCO)												
2[19]	randomized trials	no serious limitations	no serious inconsistency	serious[20]	serious[21]	None	211/390 (54.1%)	197/384 (51.3%)	RR 1.05 (0.93 to 1.2)	26 more per 1000 (from 36 fewer to 103 more)	LOW	IMPORTANT
								52%		26 more per 1000 (from 36 fewer to 104 more)		

[1] All studies reported 12 week outcomes except Rubio et al, 2001 (52 weeks).
[2] Morley et al, 2006, Kiefer 2003, Rubio 2001, Laaksonen 2008.
[3] I squared = 53%.
[4] All studies had intensive psychosocial treatment components (that may be difficult to replicate in primary care).
[5] Original analysis Revman, MH test, random effects.
[6] Morley et al, 2006; Kiefer et al, 2003; Rubio et al, 2001; Laaksonen et al, 2008; Anton et al, 2006.
[7] I squared = 59%.
[8] 4/5 studies had intensive psychosocial treatment components (that may be difficult to replicate in primary care). Anton et al, 2006 showed no difference between cognitive behavioural interventions and medical management group.
[9] 2 studies 12 weeks, Rubio et al, 2001 52 weeks.
[10] Morley et al, 2006; Rubio et al, 2001; Laaksonen et al, 2008.
[11] No explanation was provided.
[12] All studies used intensive psychosocial treatment in specialist centres.
[13] Morley et al, 2006; Rubio et al, 2001; Laaksonen et al, 2008.
[14] I squared = 86%.
[15] All studies intensive psychosocial interventions in specialist settings.
[16] Morley et al, 2006; Rubio et al, 2001; Laaksonen et al, 2008; Anton et al, 2006.
[17] I squared = 73%.
[18] 3/4 studies had intensive psychosocial treatment also. Anton 2006 no difference in medical management vs. cognitive behavioural interventions.
[19] Anton et al, 2006; Laaksonen et al, 2008.
[20] Specialist settings, with cognitive behavioural interventions in most subjects. Anton et al, 2006 no difference in medical intervention only v cognitive behavioural intervention groups.
[21] Outcome measures not validated in Anton 2006, and different measure used in Laaksonen et al, 2008 (SADD).

Table 5

Author(s): N Lintzeris, N Clark
Date: 2009-08-10
Question: Should naltrexone vs. disulfiram be used for alcohol dependence?
Settings:
Bibliography: Lintzeris N, Clark N. Naltrexone versus disulfiram for alcohol dependence (in press)

Quality assessment	**Summary of findings**			**Importance**
	No of patients	**Effect**	**Quality**	

[Preventing relapse in alcohol dependent patients]

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone	disulfiram	Relative (95% CI)	Absolute		
% abstinent (follow-up 12-52 weeks)												
3[1]	randomized trials	serious[2]	serious[3]	no serious indirectness[4]	no serious imprecision	none	91/190 (47.9%)	138/197 (70.1%) 77.3%	RR 0.68 (0.49 to 0.94)	224 fewer per 1000 (from 42 fewer to 357 fewer) 247 fewer per 1000 (from 46 fewer to 394 fewer)	LOW	IMPORTANT
% relapsed												
2[5]	randomized trials	serious[6]	very serious[7]	no serious indirectness	serious[8]	none	75/131 (57.3%)	40/131 (30.5%) 27.4%	RR 2.27 (0.8 to 6.46)	388 more per 1000 (from 61 fewer to 1667 more) 348 more per 1000 (from 55 fewer to 1496 more)	VERY LOW	CRITICAL
Time to first drink (days) (Better indicated by lower values)												
3[9]	randomized trials	serious[10]	very serious[11]	serious[12,13]	no serious imprecision	none	190	197	-	MD 25.11 lower (53.05 lower to 2.82 higher)	VERY LOW	IMPORTANT
Time to first relapse (days) (Better indicated by lower values)												
2[14]	randomized trials	serious[15]	very serious[16]	no serious indirectness	no serious imprecision	none	131	131	-	MD 40.06 lower (70.82 to 9.29 lower)	VERY LOW	IMPORTANT
Proportion abstinent days (%) (Better indicated by lower values)												
2[17]	randomized trials	serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	131	-	MD 23.23 lower (29.53 to 16.93 lower)	MODERATE	IMPORTANT
adverse effects (follow-up 12-52 weeks)												
3[1]	randomized trials	very serious[19]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/179 (0.6%)[20]	4/177 (2.3%)[21]	RR 0.32 (0.05 to 2.06)	15 fewer per 1000 (from 21 fewer to 24 more)	VERY LOW	IMPORTANT

								0%		0 fewer per 1000 (from 0 fewer to 0 more)		

[1] Petrakis et al, 2005; Laaksonen et al, 2008; DeSousa 2004.
[2] Not masked.
[3] I squared = 72%.
[4] One Finnish study used doctor delivered psychosocial intervention. One study conducted in India .
[5] Laaksonen et al, 2008; DeSousa2004.
[6] Not masked.
[7] I squared = 86% .
[8] Wide confidence intervals.
[9] Laaksonen et al, 2008; Petrakis et al, 2005; DeSousa2004.
[10] Not masked.
[11] I squared = 96%.
[12] I squared = 96%.
[13] One study in India, one study in Finland delivered by doctors in specialist settings, Petrakis et al, 2005 enrolled alcohol & psychiatric co-morbidity patients.
[14] Laaksonen et al, 2008; DeSousa 2004.
[15] Not masked.
[16] I squared = 95%.
[17] Laaksonen et al, 2008; DeSousa 2004
[18] Not masked.
[19] Loss to follow up greater than 30% in one study. Outcome assessment not blinded in one other study.
[20] Suspected cardiac death.
[21] One traffic accident. 2 psychiatric admissions and one neuropathy.

Table 6

Author(s):
Date: 2009-08-10
Question: Should acamprosate vs. disulfiram be used for alcohol dependence?
Settings:
Bibliography: Lintzeris N, Clark N. Acamprosate versus disulfiram for alcohol dependence (in press).

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	acamprosate	disulfiram	Relative (95% CI)	Absolute		

[Preventing relapse in alcohol dependent patients]

Abstinence (%) (follow-up 3 to 8 months)												
2[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	54/131 (41.2%)	86/131 (65.6%) 69.9%	RR 0.62 (0.44 to 0.87)	249 fewer per 1000 (from 85 fewer to 368 fewer) 266 fewer per 1000 (from 91 fewer to 391 fewer)	VERY LOW	IMPORTANT
relapsed % (follow-up 3-8 months)												
2	randomized trials	very serious[2]	very serious[4]	no serious indirectness	serious[5]	none	71/131 (54.2%)	39/131 (29.8%) 26.4%	RR 2.33 (0.67 to 8.06)	396 more per 1000 (from 98 fewer to 2102 more) 351 more per 1000 (from 87 fewer to 1864 more)	VERY LOW	CRITICAL
Time to first drink (Better indicated by higher values)												
2	randomized trials	very serious[2]	very serious[6]	no serious indirectness	no serious imprecision	none	131	131	-	MD 41.34 lower (85.44 lower to 2.75 higher)	VERY LOW	IMPORTANT
Time to first relapse (days) (follow-up 3-8 months; Better indicated by higher values)												
2	randomized trials	very serious[2]	serious[7]	no serious indirectness	no serious imprecision	none	131	131	-	MD 40.36 lower (62.9 to 17.82 lower)	VERY LOW	IMPORTANT
Proportion abstinent days (%) (follow-up 3-8 months; Better indicated by higher values)												
2	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	131	-	MD 23.42 lower (32.79 to 14.06 lower)	LOW	IMPORTANT
adverse effects (follow-up 3-8 months)												
2[1]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/131 (3.1%)[8]	1/131 (0.8%)[9] 0%	RR 4.16 (045 to 38.02)	24 more per 1000 (from 283 more to 336 more) 0 more per 1000 (from 0 more to	VERY LOW	IMPORTANT

										0 more)		

[1] DeSousa 2005; Laaksonen et al, 2008.
[2] Not masked.
[3] I squared = 53%.
[4] I squared = 88%.
[5] Wide confidence intervals.
[6] I squared = 98%.
[7] I squared = 93%.
[8] 4 deaths: one intoxication, 2 drownings and one suicide.
[9] One death due to a traffic accident.

Additional information that was not GRADEd

Acamprosate and naltrexone are well tolerated medications in drinkers. Bouza et al, 2004 estimated examined side effects in naltrexone vs. placebo studies, and reported higher incidence of overall adverse events (particularly gastro-intestinal and neuropsychiatric complaints) than placebo, but no greater incidence of severe AE. Only three deaths have been reported in these naltrexone v placebo studies - 2 in the naltrexone and 1 in the placebo arms (all in the same study (Landabaso et al, 1999)). Acamprosate is associated with a higher incidence of gastrointestinal side effects (mainly diarrhoea) than placebo. No deaths were reported in this review (Bouza et al, 2004). Disulfiram is associated with potentially severe adverse events (cardiac, hepatotoxicity) in individuals who continue to drink, and a clinical risk assessment should be conducted.

All three medications require high levels of medication adherence in order to maximize treatment effects. Mann et al, 2004 reviewed the controlled literature regarding acamprosate (n=20 studies), and estimated a NNT of 7.5 (95% CI=7.8 to 18.7) for abstinence after 1 year of acamprosate treatment. Bouza et al, 2004 and Srisurapanont 2002 each independently estimated a NNT of 9 (95%CI = 6-14) to prevent relapse to heavy drinking over short term (3 months) treatment. Outcomes with disulfiram are reported to be greater when disulfiram is supervised or monitored by family, friends or treatment personnel (Brewer, 2005). This has been incorporated into several trials in India (DeSousa 2004; 2005; 2008) to good effect, and may be culturally appropriate in certain communities.

Both naltrexone and acamprosate are relatively expensive medications, compared to disulfiram, which is considerably less expensive and may be more readily accessible in low-income populations (DeSousa 2004).

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From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	Acamprosate, naltrexone and disulfiram are effective compared to placebo in reducing relapse to heavy alcohol use, and other measures of alcohol consumption (e.g. number of drinking days, abstinence), and with comparable NNT to achieve these outcomes (between 7 to 9) In comparative trials, naltrexone and acamprosate are comparable, and disulfiram was associated with better outcomes than either naltrexone or acamprosate alone. There were no significant differences in severe adverse events. While acamprosate and naltrexone are well tolerated medications in drinkers, disulfiram is associated with potentially severe adverse events (cardiac, hepatotoxicity) in individuals who continue to drink.
Summary of the quality of evidence	In most analyses, the quality of the evidence was very low or low. This was related to small number of studies, heterogeneity in outcomes, poor follow up rates, lack of masking in outcome assessment and conduct in specialist settings, in which intensive psychosocial interventions accompanied the medications. Several studies however have been conducted in relevant settings (India, Korea, Brazil), suggesting that these interventions are feasible in these settings.
Balance of benefits versus harms	Side effect profile is generally acceptable with acamprosate, naltrexone and disulfiram. Patient and carer (i.e. family) education regarding potential adverse events with disulfiram is important. There was no clear evidence of higher rate of drug related adverse events with disulfiram, although there some admissions to psychiatric hospitals and neuropathies reported. The balance of benefits versus harms in non specialized settings in unclear.
Define the values and preferences including any variability and human rights issues	
Define the costs and resource use	Disulfiram is considerably less expensive than acamprosate or naltrexone.

and any other relevant feasibility issues	Disulfiram may be particularly well suited to social contexts in which the patient's immediate community networks (e.g. carers, family) can be engaged in monitoring medication adherence, as highlighted in studies from India (DeSousa 2004, DeSousa 2005).

Final recommendation(s)

Acamprosate, disulfiram or naltrexone should be offered as part of treatment to reduce relapse to heavy alcohol use in alcohol dependent patients. The decision to use acamprosate, disulfiram or naltrexone should be made taking into consideration patient preferences and availability.
Strength of recommendation: STRONG

Disulfiram should be offered to motivated patients in whom medication adherence can be monitored by treatment personnel, carers or family members, and when non-specialist health care providers are alert to potential adverse effects, including the disulfiram-alcohol reaction.
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:

Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2. (**Edited (no change to conclusions), published in Issue 2, 2011**.)

Turnbull C,OsbornDA.Home visits during pregnancy and after birth for women with an alcohol or drug problem. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD004456. DOI: 10.1002/14651858.CD004456.pub3. (**New search for studies and content updated (no change to conclusions), published in Issue 1, 2012**)