Appendix 18d: pharmacological interventions GRADE tables

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Acamprosate versus placebo

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acamprosate	Placebo	Relative (95% CI)	Absolute		
Discontinuation for any reason												
15	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	914/2005 (45.6%)	1022/2032 (50.3%)	RR 0.90 (0.81 to 0.99)	50 fewer per 1000 (from 5 fewer to 96 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 fewer per 1,000		
Discontinuation due to adverse event												
12	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	87/1890 (4.6%)	65/1910 (3.4%)	RR 1.36 (0.99 to 1.88)	12 more per 1000 (from 0 fewer to 30 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Lapsed (individuals drinking any alcohol) - at 8 weeks												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	27/72 (37.5%)	22/70 (31.4%)	RR 1.19 (0.76 to 1.88)	60 more per 1000 (from 75 fewer to 276 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		

Lapsed (individuals drinking any alcohol) - at 3 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	102/173 (59%)	118/177 (66.7%) 0%	RR 0.88 (0.75 to 1.04)	80 fewer per 1000 (from 167 fewer to 27 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Lapsed (individuals drinking any alcohol) - at 6 months												
17	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1337/2013 (66.4%)	1534/1951 (78.6%) 0%	RR 0.83 (0.77 to 0.88)	134 fewer per 1000 (from 94 fewer to 181 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Lapsed (individuals drinking any alcohol) - at 12 months												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	515/661 (77.9%)	601/671 (89.6%) 0%	RR 0.88 (0.8 to 0.96)	108 fewer per 1000 (from 36 fewer to 179 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Lapsed (individuals drinking any alcohol) - at 18 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	148/173 (85.5%)	161/177 (91%) 0%	RR 0.94 (0.87 to 1.02)	55 fewer per 1000 (from 118 fewer to 18 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Lapsed (individuals drinking any alcohol) - at 24 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	197/224 (87.9%)	213/224 (95.1%)	RR 0.92 (0.87 to 0.98)	76 fewer per 1000 (from 19 fewer to 124 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

								0%		0 fewer per 1,000		
Relapsed to heavy drinking - at 3 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	211/303 (69.6%)	226/309 (73.1%)	RR 0.95 (0.86 to 1.05)	37 fewer per 1000 (from 102 fewer to 37 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 fewer per 1,000		
Relapsed to heavy drinking - at 6 months												
10	Randomised trials	No serious limitations	Serious[3]	No serious indirectness	No serious imprecision	None	802/1357 (59.1%)	912/1297 (70.3%)	RR 0.81 (0.72 to 0.92)	134 fewer per 1000 (from 56 fewer to 197 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 fewer per 1,000		
Relapsed to heavy drinking - at 12 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	240/303 (79.2%)	255/309 (82.5%)	RR 0.96 (0.89 to 1.04)	33 fewer per 1000 (from 91 fewer to 33 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 fewer per 1,000		
Percentage of days abstinent - at 8 weeks (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	72	70	-	SMD -0.10 (-0.43 to 0.23)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	303	309	-	SMD 0.00 (-0.2 to 0.2)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 3 months (Better indicated by lower values)												
1	Randomised	No serious	No serious	No serious	No serious	None	303	309	-	SMD 0.00 (-0.16	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision					to 0.15)	HIGH	
Cumulative abstinence duration - over 3 months (Better indicated by lower values)												
2	Randomised trials	No serious limitations	Serious[3]	No serious indirectness	Serious[4]	None	118	123	-	SMD -2.75 (-7.51 to 2.01)	⊕⊕OO LOW	CRITICAL
Cumulative abstinence duration - over 6 months (Better indicated by lower values)												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	562	572	-	SMD -0.29 (-0.41 to -0.17)	⊕⊕⊕⊕ HIGH	CRITICAL
Cumulative abstinence duration - over 9 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	164	166	-	SMD -0.24 (-0.46 to -0.03)	⊕⊕⊕⊕ HIGH	CRITICAL
Cumulative abstinence duration - over 12 months (Better indicated by lower values)												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	655	661	-	SMD -0.35 (-0.46 to -0.24)	⊕⊕⊕⊕ HIGH	CRITICAL
Cumulative abstinence duration - over 24 months (Better indicated by lower values)												
2	Randomised trials	No serious limitations	Serious[3]	No serious indirectness	No serious imprecision	None	360	360	-	SMD -0.34 (-0.66 to -0.03)	⊕⊕⊕O MODERATE	CRITICAL
Time in days to first drink (Better indicated by lower values)												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	364	374	-	SMD -0.26 (-0.45 to -0.06)	⊕⊕⊕⊕ HIGH	CRITICAL
DDD (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	127	131	-	SMD -0.05 (-0.29 to 0.2)	⊕⊕⊕⊕ HIGH	CRITICAL

Percentage of days without heavy drinking (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	72	70	-	SMD -0.06 (-0.38 to 0.27)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] 95% CI includes no effect and RR increase greater than 25%.

[2] 95% CI includes no effect and RR decrease greater than 25%.

[3] Heterogeneity >75%.

[4] 95% CI includes no effect. Upper and lower confidence limit crosses an effect size of 0.5 in both directions

Economic profile

Acamprosate versus usual care/placebo

Study & country	Limitations	Applicability	Other comments	Incremental cost (£)	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Annemans *et al.*, 2000 Belgium	Potentially serious limitations[1]	Partially applicable[2]	Costing analysis. Treatment effect outcomes reported as well. Time horizon: 24 months	-577[3]	7% abstinent	-82 / percentage of patients remaining abstinent	The sensitivity analysis looked at the proportion of patients followed up in an institution following detoxification (base case value: 0.541), the cost of acute hospitalisation and the effectiveness of acamprosate, expressed as the probability of relapse at 3 months (base case value: 0.586). Acamprosate was shown to be cost saving at a follow-up rate of =>24%, at hospitalisation costs of =>50% of actual costs, and at relapse rates <= 59%. This was the most sensitive estimate.
Guideline economic analysis UK	Minor limitations[4]	Directly applicable	Cost-utility analysis based on decision model. Time horizon 12 months.	139	0.027	5,043 / QALY	Probabilistic sensitivity analysis: at a cost-effectiveness threshold range of £20-30,000, the probability of acamprosate being most the cost-effective treatment was 52-53%.

[1] Belgian population and healthcare system. Effectiveness estimates from several sources: Whitworth *et al.*, 1996, NEAT study unpublished data.

[2] Conducted in Belgium – Institute of Health Insurance perspective; no QALYs estimated but health outcome measure may be relevant.

[3] Converted from 1997 German Euros using a Purchasing Power Parity (PPP) exchange rate of 0.89 (www.oecd.org/std/ppp) then inflated using HCHS indices (Curtis, 2009)

[4] Short time horizon (12 months); clinical efficacy data based on network meta-analysis subject to a number of assumptions.

Palmer *et al.*, 2000 Germany	Potentially serious limitations[5]	Partially applicable[6]	Markov model simulating the progression of important complications. Time horizon: lifetime (5% discount rate)	-1672[7]	0.52 Life year gained	-3 216 / Life year gained	The sensitivity analyses suggested that, on the life expectancy side, the probabilities of hepatic disease, suicide and relapse rate had the greatest impact on the study results. On the cost side, the probability of relapse in the first year, suicide at age 45, various liver complications, alcohol psychosis, and the costs of treatment of chronic pancreatitis and alcohol dependence, had the greatest impact on the study results.
Rychlik *et al.*, 2003 Germany	Potentially serious limitations[8]	Partially applicable[9]	Cost-effective analysis. Average cost ratios reported as costs per abstinent rate	-342[10]	Additional 12% of cohort abstinent over 12 months	-2 853 / % of cohort abstinent over 12 months	No sensitivity analysis
Schadlich & Brecht, 1998 Germany	Potentially serious limitations[11]	Partially applicable[12]	Cost-effective analysis. Average cost ratios reported. Time horizon: 48 weeks of treatment and 48 weeks of follow-up	-59 9421[13]	226 additional patients who were abstinent	-2 652/ [14]additional abstinent patient	-414 to -9002/ additional abstinent patient (Lower and upper cost boundary) Acamprosate was found to be cost saving in 78% of the scenarios tested. The parameter with the greatest impact on results was the rate of abstinence under acamprosate therapy.

[5] Data used to estimate costs and effects are not reported or described adequately. This may potentially bias results. Funded by industry.
[6] Conducted in Germany – health insurance perspective; no QALYs estimated but health outcome measure may be relevant.
[7] Converted from 1996 German DM using a PPP exchange rate of 0.99 (www.oecd.org/std/ppp) then inflated by using HCHS indices (Curtis, 2009).
[8] German population and healthcare system. Results not subject to sensitivity analysis, effectiveness data based on naturalistic study. Funded by industry.
[9] Conducted in Germany – health insurance perspective; cost year not clear, no QALYs estimated but health outcome measure may be relevant.
[10] Converted from 1998 German Euro using a PPP exchange rate of 0.88 (www.oecd.org/std/ppp) then inflated using HCHS indices (Curtis, 2009).
[11] Some uncertainty over the applicability of German trial data (PRAMA study) to the UK. May be differences in population as well as healthcare resource use and unit costs in Germany. Efficacy data derived selectively from PRAMA study. Funded by industry.
[12] Conducted in Germany – German health care system perspective; no QALYs estimated but health outcome measure may be relevant.
[13] Converted from 1995 German DM using a PPP exchange rate of 1.00 (www.oecd.org/std/ppp) then inflated using HCHS indices (Curtis, 2009).
[14] Negative ICER indicates that intervention is dominant, that is, cheaper and more effective.

Slattery *et al.*, 2003 Scotland	Minor limitations [15]	Partially applicable[16]	Effectiveness data based on SIGN meta-analysis and combined with Scottish NHS cost data. 12 months of drug treatment	-10 3713[17]	84 additional patients abstinent	-1 237 / additional abstinent patient	4643 – -3477/ additional abstinent patient: range in one way sensitivity analysis

[15] Some limitations in reporting e.g. sources of effectiveness data not explicitly stated. However, costings based on Scottish NHS perspective. Measure of benefit does not follow NICE reference case, however the health outcome may be relevant

[16] Some uncertainty over the applicability of trial data to the UK because of differences in populations and severity. However, resources use, costs and perspectives are Scottish-UK specific. However the discount rate does not follow the NICE reference case.

[17] 2002 Scottish pounds inflated using HCHS indices (Curtis, 2009)

Naltrexone versus placebo

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone	Placebo	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
25	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	694/2135 (32.5%)	653/1898 (34.4%) 0%	RR 0.94 (0.84 to 1.05)	21 fewer per 1000 (from 55 fewer to 17 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinued treatment - due to adverse effects												
12	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	58/976 (5.9%)	26/957 (2.7%) 0%	RR 1.79 (1.15 to 2.77)	21 more per 1000 (from 4 more to 48 more) 0 more per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Lapsed (individuals drinking any alcohol) - at 3 months												
17	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	613/946 (64.8%)	669/947 (70.6%) 0%	RR 0.92 (0.86 to 1)	56 fewer per 1000 (from 99 fewer to 0 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Lapsed (individuals drinking any alcohol) - at 6 months of maintenance treatment												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	30/56 (53.6%)	39/57 (68.4%) 0%	RR 0.79 (0.6 to 1.05)	144 fewer per 1000 (from 274 fewer to 34 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL

Lapsed (individuals drinking any alcohol) - at 6-month follow-up												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	31/40 (77.5%)	34/40 (85%) 0%	RR 0.90 (0.69 to 1.17)	85 fewer per 1000 (from 264 fewer to 144 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking - at 3 months												
22	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	841/1766 (47.6%)	904/1554 (58.2%) 0%	RR 0.83 (0.76 to 0.91)	99 fewer per 1000 (from 52 fewer to 140 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Relapsed to heavy drinking - at 6 months' endpoint												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	73/120 (60.8%)	76/120 (63.3%) 0%	RR 0.96 (0.79 to 1.17)	25 fewer per 1000 (from 133 fewer to 108 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking - at 6-month follow-up												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	71/146 (48.6%)	93/138 (67.4%) 0%	RR 0.74 (0.6 to 0.9)	175 fewer per 1000 (from 67 fewer to 270 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Relapsed to heavy drinking - at 6 months' maintenance treatment												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/56 (17.9%)	22/57 (38.6%) 0%	RR 0.46 (0.24 to 0.89)	208 fewer per 1000 (from 42 fewer to 293 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL

Relapsed to heavy drinking - at 9 months' endpoint												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	32/58 (55.2%)	43/58 (74.1%) 0%	RR 0.74 (0.56 to 0.98)	193 fewer per 1000 (from 15 fewer to 326 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Relapsed to heavy drinking - at 12-month follow-up												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	243/309 (78.6%)	255/309 (82.5%) 0%	RR 0.95 (0.88 to 1.03)	41 fewer per 1000 (from 99 fewer to 25 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 3 months (Better indicated by lower values)												
9	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	798	809	-	SMD -0.22 (-0.37 to -0.07)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 6 months (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	122	115	-	SMD -0.25 (-0.51 to 0)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	309	309	-	SMD -0.11 (-0.42 to 0.2)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first drink (Better indicated by lower values)												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	362	368	-	SMD -0.07 (-0.21 to 0.08)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first heavy drinking episode (Better indicated by lower values)												

8	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	Serious[3]	None	845	668	-	SMD -0.32 (-0.68 to 0.03)	⊕⊕OO LOW	CRITICAL
Cumulative abstinence duration (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	102	115	-	SMD -0.12 (-0.39 to 0.15)	⊕⊕⊕⊕ HIGH	CRITICAL
Drinks per drinking day in study period (Better indicated by lower values)												
10	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	910	729	-	SMD -0.28 (-0.44 to -0.11)	⊕⊕⊕⊕ HIGH	CRITICAL
Heavy drinking episodes during study period (Better indicated by lower values)												
7	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	No serious imprecision	None	391	406	-	SMD -0.43 (-0.82 to -0.03)	⊕⊕⊕O MODERATE	CRITICAL
Total drinks consumed during study period (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	126	131	-	SMD -0.32 (-0.7 to 0.06)	⊕⊕⊕O MODERATE	CRITICAL

[1] 95% CI includes no effect and RR reduction greater than 25%.

[2] Heterogeneity >75%.

[3] 95% CI includes no effect and low confidence limit cross effect size of 0.5.

Economic profile

Naltrexone versus placebo/usual care

Study & country	Limitations	Applicability	Other comments	Incremental cost (£)	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Mortimer & Segal, 2005 Australia	Potentially serious limitations[18]	Partially applicable[19]	Uses Markov modelling Only study to use QALYs as measure of benefit. Time horizon: lifetime	404[20]	0.0528	7647/QALY	2196 - ∞ £/ QALY range in one way sensitivity analysis
Guideline economic analysis UK	Minor limitations[21]	Directly applicable	Cost-utility analysis based on decision model. Time horizon 12 months	133	0.024	5,395 / QALY	Probabilistic sensitivity analysis: at a cost-effectiveness threshold range of £20-30,000, the probability of naltrexone being most the cost-effective treatment was 44-45%
Slattery *et al.*, 2003 Scotland	Minor limitations [22]	Partially applicable[23]	Effectiveness data based on SIGN meta-analysis and combined with Scottish NHS cost data. 6 months of treatment	125 536[24]	55	2 289/ additional abstinent patient	29 476 – -2945/ additional abstinent patient: range in one way sensitivity analysis

[18] Some uncertainty over applicability of the study to the UK due to potential differences in populations. Effectiveness data sourced from Streeton, C. & Whelan, G. (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. *Alcohol and Alcoholism, 36*, 544-552. Perspective of the Department of Health and Ageing adopted. 5% discount rate used, which is not in keeping with NICE reference case. Sources of certain data, for example, nit costs not explicit.

[19] This is the only study that reports QALYs. However, the source and methods of determining the utility data was not adequately described.

[20] Converted from 2003 AUS$ using a PPP exchange rate of 1.35 (www.oecd.org/std/ppp) then inflated using HCHS indices (Curtis, 2009).

[21] Short time horizon (12 months); clinical efficacy data based on network meta-analysis subject to a number of assumptions.

[22] Some limitations in reporting for example, sources of effectiveness data not explicitly stated. However, costings based on Scottish NHS perspective. Measure of benefit does not follow NICE reference case, however the health outcome may be relevant.

[23] Some uncertainty over the applicability of trial data to UK because of differences in populations and severity. However, resources use, costs and perspectives are Scottish-UK specific. However the discount rate does not follow the NICE reference case.

[24] 2002 Scottish pounds inflated using HCHS indices (Curtis, 2009)

Naltrexone versus acamprosate

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone	Acamprosate	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	151/479 (31.5%)	178/478 (37.2%) 0%	RR 0.85 (0.72 to 1.01)	56 fewer per 1000 (from 104 fewer to 4 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Discontinued treatment - due to adverse events												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[2]	None	14/386 (3.6%)	9/383 (2.3%) 0%	RR 1.44 (0.63 to 3.29)	10 more per 1000 (from 9 fewer to 53 more) 0 more per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Lapsed (individuals drinking any alcohol) - at 12 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/77 (58.4%)	66/80 (82.5%) 0%	RR 0.71 (0.57 to 0.88)	239 fewer per 1000 (from 99 fewer to 355 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Relapsed to heavy drinking - at 3 months endpoint												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	260/402 (64.7%)	271/398 (68.1%) 0%	RR 0.96 (0.87 to 1.06)	27 fewer per 1000 (from 89 fewer to 41 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL

Relapsed to heavy drinking - at 6-month follow-up												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[3]	None	21/40 (52.5%)	22/40 (55%) 0%	RR 0.95 (0.64 to 1.43)	28 fewer per 1000 (from 198 fewer to 236 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking - at 12 months' endpoint												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	243/309 (78.6%)	240/303 (79.2%) 0%	RR 0.99 (0.91 to 1.08)	8 fewer per 1000 (from 71 fewer to 63 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - over 3 months (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	362	358	-	SMD 0.04 (-21 to 0.29)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - over 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	309	303	-	SMD -0.11 (-0.27 to 0.04)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first drink (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	130	135	-	SMD -0.09 (-0.34 to 0.15)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first heavy drinking episode (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	130	135	-	SMD -0.39 (-0.81 to 0.03)	⊕⊕⊕O MODERATE	CRITICAL
DDD (Better indicated by lower values)												
1	Randomised	No serious	No serious	No serious	No serious	None	77	80	-	SMD -0.76 (-1.09	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision					to -0.44)	HIGH	

[1] 95% CI includes no effect and RR reduction >25%.

[2] 95% CI includes no effect and RR increase >25%.

[3] 95% CI includes no effect and RR increase and decrease greater than 25%.

[4] 95% CI includes no effect and lower confidence limit crosses effect size of 0.5.

Economic profile

Naltrexone versus acamprosate

Study & country	Limitations	Applicability	Other comments	Incremental cost (£)	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Guideline economic analysis UK	Minor limitations[25]	Directly applicable	Cost-utility analysis based on decision model. Time horizon: 12 months	5	0.003	1,899 / QALY	Probabilistic sensitivity analysis: at a cost-effectiveness threshold range of £20-30,000, the probability of acamprosate being the most cost-effective treatment was 52-53%

[25] Short time horizon (12 months); clinical efficacy data based on network meta-analysis subject to a number of assumptions (see Chapter 7).

Naltrexone + sertraline versus naltrexone

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone + sertraline	Naltrexone	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	35/90 (38.9%)	22/88 (25%) 0%	RR 1.55 (1 to 2.42)	137 more per 1000 (from 0 more to 355 more) 0 more per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinued treatment - due to adverse events												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	9/90 (10%)	3/88 (3.4%) 0%	RR 2.92 (0.82 to 10.44)	65 more per 1000 (from 6 fewer to 321 more) 0 more per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Lapsed (individuals drinking any alcohol)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	23/33 (69.7%)	22/34 (64.7%) 0%	RR 1.08 (0.77 to 1.51)	52 more per 1000 (from 149 fewer to 330 more) 0 more per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	22/33 (66.7%)	22/34 (64.7%)	RR 1.03 (0.73 to	19 more per 1000 (from 175 fewer to 298	⊕⊕⊕O MODERATE	CRITICAL

									1.46)	more)		
								0%		0 more per 1,000		
Percentage of days abstinent (Better indicated by lower values)												
2	Randomised trials	No serious limitations	serious[3]	No serious indirectness	Serious[4]	None	90	88	-	SMD -0.12 (-0.79 to 0.56)	⊕⊕OO LOW	CRITICAL
DDD during study period (Better indicated by lower values)												
2	Randomised trials	No serious limitations	serious[3]	No serious indirectness	Serious[4]	None	87	91	-	SMD -0.95 (-2.94 to 1.04)	⊕⊕OO LOW	CRITICAL
Percentage of days heavy drinking during study period (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[5]	None	33	34	-	SMD -0.23 (-0.71 to 0.25)	⊕⊕⊕O MODERATE	CRITICAL

[1] 95% CI includes no effect and RR increase greater than 25%.

[2] 95% CI crosses line of no effect and RR decrease and increase greater than 25%.

[3] Heterogeneity >75%.

[4] 95% CI includes no effect and upper and low confidence limits cross an effect size of 0.5.

[5] 95% CI includes no effect and lower confidence limits cross an effect size of 0.5.

Naltrexone versus topiramate

Quality assessment							**Summary of findings**					**Importance**
							No. of patients		**Effect**		**Quality**	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Naltrexone**	**Topiramate**	**Relative (95% CI)**	**Absolute**		
Discontinued treatment - for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	20/49 (40.8%)	19/52 (36.5%)	RR 1.12 (0.68 to 1.83)	44 more per 1000 (from 117 fewer to 303 more)	⊕⊕⊕O MODERATE	CRITICAL

								0%		0 more per 1,000		
Lapsed (individuals drinking any alcohol) - at 1 month												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	23/49 (46.9%)	17/52 (32.7%)	RR 1.44 (0.88 to 2.35)	144 more per 1000 (from 39 fewer to 441 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Lapsed (individuals drinking any alcohol) - at 2 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	29/49 (59.2%)	20/52 (38.5%)	RR 1.54 (1.02 to 2.33)	208 more per 1000 (from 8 more to 512 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 more per 1,000		
Lapsed (individuals drinking any alcohol) - at 3 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious	None	39/49 (79.6%)	28/52 (53.8%)	RR 1.48 (1.11 to 1.97)	258 more per 1000 (from 59 more to 522 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Cumulative abstinence duration (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	49	52	-	SMD 0.34 (-0.06 to 0.73)	⊕⊕⊕O MODERATE	CRITICAL
Time to first heavy drinking day (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	49	52	-	SMD 0.43 (0.04 to 0.83)	⊕⊕⊕⊕ HIGH	CRITICAL
Heavy drinking weeks during the study period (Better indicated by lower values)												
1	Randomised	No serious	No serious	No serious	Serious[3]	None	49	52	-	SMD 0.33 (-0.06	⊕⊕⊕O	CRITICAL

	trials	limitations	inconsistency	indirectness						to 0.72)	MODERATE	

[1] 95% CI includes no effect, RR increase and decrease >25%.

[2] 95% CI includes no effect, RR increase greater than 25%.

[3] 95% CI includes no effect and upper confidence limit crosses an effect size of 0.5.

Naltrexone + acamprosate versus placebo

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Naltrexone + acamprosate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Discontinued treatment - leaving for any reason												
2	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	Serious[2]	None	138/345 (40%)	118/349 (33.8%)	RR 1.00 (0.53 to 1.9)	0 fewer per 1000 (from 159 fewer to 304 more)	⊕⊕OO LOW	CRITICAL
								0%		0 fewer per 1,000		
Discontinued treatment- due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/305 (4.3%)	4/309 (1.3%)	RR 3.16 (1.03 to 9.76)	28 more per 1000 (from 0 more to 114 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 more per 1,000		
Relapsed to heavy drinking - at 3 months												
2	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	Serious[3]	None	223/345 (64.6%)	256/349 (73.4%)	RR 0.78 (0.56 to 1.09)	161 fewer per 1000 (from 323 fewer to 66 more)	⊕⊕OO LOW	CRITICAL
								0%		0 fewer per 1,000		

Relapsed to heavy drinking - at 6 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/40 (35%)	32/40 (80%) 0%	RR 0.44 (0.28 to 0.69)	448 fewer per 1000 (from 248 fewer to 576 fewer) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Relapsed to heavy drinking - at 12 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	245/305 (80.3%)	255/309 (82.5%) 0%	RR 0.97 (0.9 to 1.05)	25 fewer per 1000 (from 83 fewer to 41 more) 0 fewer per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 3 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	305	309	-	SMD -0.09 (-0.42 to 0.25)	⊕⊕⊕O MODERATE	CRITICAL
Percentage of days abstinent - at 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	309	-	SMD -0.09 (-0.25 to 0.06)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Heterogeneity >75%

[2] 95% CI includes no effect, RR increase and decrease greater than 25%

[3] 95% CI includes no effect, RR decrease greater than 25%

Naltrexone + acamprosate versus acamprosate

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone + acamprosate	Acamprosate	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	138/345 (40%)	139/342 (40.6%)	RR 0.92 (0.65 to 1.32)	32 fewer per 1000 (from 142 fewer to 130 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 fewer per 1,000		
Discontinued treatment - due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	13/305 (4.3%)	9/303 (3%)	RR 1.39 (0.34 to 5.71)	12 more per 1000 (from 20 fewer to 141 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Relapsed to heavy drinking - at 3 months												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	223/345 (64.6%)	231/343 (67.3%)	RR 0.93 (0.74 to 1.17)	47 fewer per 1000 (from 175 fewer to 114 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 fewer per 1,000		

Relapsed to heavy drinking - at 6 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	14/40 (35%)	22/40 (55%) 0%	RR 0.64 (0.38 to 1.06)	198 fewer per 1000 (from 341 fewer to 33 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking - at 12 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	245/305 (80.3%)	240/303 (79.2%) 0%	RR 1.02 (0.94 to 1.1)	16 more per 1000 (from 48 fewer to 79 more) 0 more per 1,000	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 3 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	303	-	SMD -0.08 (-0.29 to 0.13)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	303	-	SMD -0.11 (-0.27 to 0.05)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] 95% CI includes no effect, RR increase and decrease greater than 25%.

[2] 95% CI includes no effect, RR decrease greater than 25%.

Naltrexone + acamprosate versus naltrexone

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Naltrexone + acamprosate	Naltrexone	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	138/345 (40%)	126/349 (36.1%)	RR 1.09 (0.87 to 1.37)	32 more per 1000 (from 47 fewer to 134 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Discontinued treatment - due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	13/305 (4.3%)	12/309 (3.9%)	RR 1.10 (0.5 to 2.4)	4 more per 1000 (from 20 fewer to 55 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Relapsed to heavy drinking - at 3 months												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	223/345 (64.6%)	221/349 (63.3%)	RR 1.03 (0.9 to 1.17)	19 more per 1000 (from 63 fewer to 108 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 more per 1,000		
Relapsed to heavy drinking - at 6 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	14/40 (35%)	21/40 (52.5%)	RR 0.67 (0.4 to	173 fewer per 1000 (from 315 fewer to 63	⊕⊕⊕O MODERATE	CRITICAL

									1.12)	more)		
								0%		0 fewer per 1,000		
Relapsed to heavy drinking - at 12 months												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	245/305 (80.3%)	243/307 (79.2%)	RR 1.02 (0.94 to 1.1)	16 more per 1000 (from 48 fewer to 79 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 more per 1,000		
Percentage of days abstinent - at 3 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	309	-	SMD -0.04 (-0.2 to 0.12)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage of days abstinent - at 12 months (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	309	-	SMD 0.02 (-0.18 to 0.21)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] 95% CI includes no effect and RR increase greater than 25%.

[2] 95% CI includes no effect and RR increase and decrease greater than 25%.

[3] 95% CI includes no effect and RR decrease greater than 25%.

Disulfiram versus placebo

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Disulfiram	placebo	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	8/202 (4%)	7/204 (3.4%)	RR 1.15 (0.43 to 3.12)	5 more per 1000 (from 19 fewer to 72 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 more per 1,000		
Lapsed (individuals drinking any alcohol)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	198/245 (80.8%)	190/247 (76.9%)	RR 1.05 (0.96 to 1.15)	38 more per 1000 (from 31 fewer to 115 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		0 more per 1,000		
Units consumed 1 month before study end - change score (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[2]	None	44	46	-	SMD -0.16 (-0.58 to 0.25)	⊕⊕⊕O MODERATE	CRITICAL
Units consumed per week - change score (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	49	48	-	SMD -0.35 (-0.75 to 0.05)	⊕⊕⊕⊕ HIGH	CRITICAL
Total units consumed in 6 months before study end - change score (Better indicated by lower values)												
1	Randomised	No serious	No serious	No serious	No serious	None	46	44	-	SMD -0.49 (-0.91	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision					to -0.07)	HIGH	
Number of days abstinent - change score (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	47	46	-	SMD -0.45 (-0.86 to -0.04)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] 95% CI includes no effect and RR increase and decrease greater than 25%.

[2] 95% CI includes no effect and lower confidence limit crosses effect size of 0.5.

Disulfiram versus acamprosate

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Disulfiram	Acamprosate	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	21/81 (25.9%)	17/81 (21%)	RR 1.24 (0.71 to 2.16)	50 more per 1000 (from 61 fewer to 244 more)	⊕⊕OO LOW	CRITICAL
								0%		0 more per 1,000		
Time to first drink (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	39	50	-	SMD -0.84 (-1.28 to -0.4)	⊕⊕⊕O MODERATE	CRITICAL
Time to first heavy drinking episode (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	33	44	-	SMD -1.17 (-1.66 to -0.68)	⊕⊕⊕O MODERATE	CRITICAL

Abstinent days per week - up to 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	54	52	-	SMD -1.11 (-1.52 to -0.7)	⊕⊕⊕O MODERATE	CRITICAL
Abstinent days per week - up to 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	43	48	-	SMD -0.74 (-1.17 to -0.31)	⊕⊕⊕O MODERATE	CRITICAL
Alcohol consumption (g/week) - up to 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	60	58	-	SMD -1.06 (-1.44 to -0.67)	⊕⊕⊕O MODERATE	CRITICAL
Alcohol consumption (g/week) - up to 12months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	37	39	-	SMD -0.66 (-1.12 to -0.2)	⊕⊕⊕O MODERATE	CRITICAL

[1] Open-label trials only.

[2] 95% CI includes no effect and RR increase and decrease greater than 25%.

Disulfiram versus naltrexone

Quality assessment							**Summary of findings**					**Importance**
							No. of patients		**Effect**		**Quality**	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Disulfiram**	**Naltrexone**	**Relative (95% CI)**	**Absolute**		
Discontinued treatment - for any reason												
2	Randomised trials	serious[1]	No serious inconsistency	No serious indirectness	serious[2]	None	23/131 (17.6%)	18/131 (13.7%)	RR 1.27 (0.73 to 2.19)	37 more per 1000 (from 37 fewer to 163 more)	⊕⊕OO LOW	CRITICAL
								0%		0 more per 1,000		

Discontinued treatment - due to adverse events												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/50 (2%)	0/50 (0%) 0%	RR 3.00 (0.13 to 71.92)	0 more per 1000 (from 0 fewer to 0 more) 0 more per 1,000	⊕⊕OO LOW	CRITICAL
Lapsed (individuals drinking any alcohol)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5/50 (10%)	28/50 (56%) 0%	RR 0.18 (0.08 to 0.42)	459 fewer per 1000 (from 325 fewer to 515 fewer) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Relapsed to heavy drinking												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/50 (14%)	25/50 (50%) 0%	RR 0.28 (0.13 to 0.59)	360 fewer per 1000 (from 205 fewer to 435 fewer) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Time to first drink (Better indicated by lower values)												
2	Randomised trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	89	100	-	SMD -1.22 (-2.47 to 0.02)	⊕⊕OO LOW	CRITICAL
Time to first heavy drinking episode (Better indicated by lower values)												
2	Randomised trials	Serious[1]	Serious[3]	No serious indirectness	No serious imprecision	None	83	97	-	SMD -1.50 (-2.49 to -0.51)	⊕⊕OO LOW	CRITICAL
Total days abstinent over 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50	50	-	SMD -0.41 (-0.81 to -0.02)	⊕⊕⊕O MODERATE	CRITICAL

Abstinent days per week - up to 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	54	53	-	SMD -1.09 (-1.5 to -0.68)	⊕⊕⊕O MODERATE	CRITICAL
Abstinent days per week - up to 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	43	48	-	SMD -0.74 (-1.17 to -0.31)	⊕⊕⊕O MODERATE	CRITICAL
Drinks per drinking day during study period (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50	50	-	SMD -0.11 (-0.5 to 0.28)	⊕⊕⊕O MODERATE	CRITICAL
Alcohol consumption (g/week) - up to 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	60	64	-	SMD -0.93 (-1.31 to -0.56)	⊕⊕⊕O MODERATE	CRITICAL
Alcohol consumption (g/week) - up to 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	37	41	-	SMD -0.74 (-1.2 to -0.28)	⊕⊕⊕O MODERATE	CRITICAL

[1] Open-label trials only.

[2] 95% CI includes no effect and RR increase and decrease greater than 25%.

[3] Heterogeneity >75%.

Disulfiram versus topiramate

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Disulfiram	Topiramate	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	4/50 (8%)	4/50 (8%) 0%	RR 1.00 (0.26 to 3.78)	0 fewer per 1000 (from 59 fewer to 222 more) 0 fewer per 1,000	⊕⊕OO LOW	CRITICAL
Discontinued treatment - due to adverse events												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/50 (0%)	2/50 (4%) 0%	RR 0.20 (0.01 to 4.06)	32 fewer per 1000 (from 40 fewer to 122 more) 0 fewer per 1,000	⊕⊕OO LOW	CRITICAL
Relapsed to heavy drinking												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5/50 (10%)	22/50 (44%) 0%	RR 0.23 (0.09 to 0.55)	339 fewer per 1000 (from 198 fewer to 400 fewer) 0 fewer per 1,000	⊕⊕⊕O MODERATE	CRITICAL
Time to first drink (Better indicated by lower values)												
1	Randomised trials	serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50	50	-	SMD -3.16 (-3.75 to -2.56)	⊕⊕⊕O MODERATE	CRITICAL

Time to first heavy drinking day (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50	50	-	SMD -2.74 (-3.29 to -2.19)	⊕⊕⊕O MODERATE	CRITICAL
Total days of abstinence during study period (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50	50	-	SMD -0.30 (-0.7 to 0.09)	⊕⊕⊕O MODERATE	CRITICAL

[1] Open-label trial

[2] 95% CI includes no effect and RR increase and decrease greater than 25%.

Economic profile

Disulfiram or combination of drugs versus placebo/usual care

Study & country	Limitations	Applicability	Other comments	Incremental cost (£)	Incremental effect (QALYs)	ICER (£/QALY)	Uncertainty
Slattery *et al.*, 2003 Scotland	Minor limitations [26]	Partially applicable[27]	Effectiveness data based on RCTs of unsupervised disulfiram therapy. Costs of supervision, however, included. 6 months of treatment	230 496[28]	38	6 103/ additional abstinent patient	40 716/ additional abstinent patient - standard care dominates: range in one way sensitivity analysis

[26] Some limitations in reporting, for example, sources of effectiveness data not explicitly stated. Furthermore, effectiveness data based on unsupervised disulfiram studies; however, costings include supervision costs. Costings are based on Scottish NHS perspective. Measure of benefit does not follow NICE reference case, however the health outcome may be relevant.

[27] Some uncertainty over the applicability of trial data to UK because of differences in populations and severity. However, resources use, costs and perspectives are Scottish-UK specific. However the discount rate does not follow the NICE reference case.

[28] 2002 prices inflated using HCHS indices (Curtis, 2009)

Zarkin *et al.*, 2008 US	Potentially serious limitations[29]	Partially applicable	Based on COMBINE study set in 11 US study centres. Nine combinations of drugs and psychological interventions compared. Results were sensitive to the price of drugs. Time horizon: 16 weeks	226[30]	0.5 % days abstinent (PDA)	452/ PDA[31]	Under the high pharmaceutical price scenario, naltrexone was approximately 3 times more expensive than the baseline case; acamprosate was approximately 15% more expensive. The results of the 2-way sensitivity analysis were the same as the 1-way analysis when pharmaceutical prices are varied.

[29] Some uncertainty over the applicability of US trial data to the UK. Differences in health care systems may result in differences in population (insured only) as well as healthcare resource use and unit costs.
[30] Converted from 2007 US $ using a PPP exchange rate of 0.65 (www.oecd.org/std/ppp) then inflated using HCHS indices (Curtis, 2009).
[31] This is the ICER for the most cost-effective intervention, that is, medical management, acamprosate and naltrexone.

Disulfiram + counselling versus counselling

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Disulfiram + counselling	Counselling	Relative (95% CI)	Absolute		
Discontinued treatment - for any reason												
1	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	10/26 (38.5%)	17/23 (73.9%)	RR 0.46 (0.08 to 2.56)	399 fewer per 1000 (from 680 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
								0%		0 fewer per 1,000		
Lapsed (individuals drinking any alcohol)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	20/26 (76.9%)	21/23 (91.3%)	RR 0.86 (0.55 to 1.34)	128 fewer per 1000 (from 411 fewer to 310 more)	⊕⊕OO LOW	CRITICAL
								0%		0 fewer per 1,000		

[1] Open-label trials only.

[2] Heterogeneity >75%.

[3] 95% CI includes no effect and RR increase and decrease greater than 25%.