



Alcohol use disorders: harmful drinking and alcohol dependence Evidence Update January 2013

A summary of selected new evidence relevant to NICE clinical guideline 115 'Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence' (2011)



Evidence Update 28

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the [NHS Evidence topic page for alcohol](#).

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction	4
Key points	5
1 Commentary on new evidence	7
1.1 Principles of care	7
1.2 Identification and assessment	8
1.3 Interventions for alcohol misuse	8
2 New evidence uncertainties.....	19
Appendix A: Methodology.....	20
Appendix B: The Evidence Update Advisory Group and Evidence Update project team	22

Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:


¹  [Alcohol use disorders: harmful drinking and alcohol dependence](#). NICE clinical guideline 115 (2011).


A search was conducted for new evidence published from 1 March 2010 to 8 August 2012. A total of 4398 pieces of evidence were identified and assessed, of which 14 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An [Evidence Update Advisory Group](#), comprised of topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

¹  [Depression: the treatment and management of depression in adults](#). NICE clinical guideline 90 (2009).

¹  [Generalised anxiety disorder and panic disorder: with or without agoraphobia in adults](#). NICE clinical guideline 113 (2011).

Quality standards


- [Alcohol dependence and harmful alcohol use](#). NICE quality standard 11 (2011)

Other relevant NICE Evidence Updates

- [Alcohol-use disorders: physical complications](#). NICE Evidence Update 10 (2012)

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

¹ NICE-accredited guidance is denoted by the Accreditation Mark 

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	No
Principles of care <ul style="list-style-type: none"> Evidence suggests that involving the family in treatment is beneficial to responding to the individual needs of family members. 		✓
Interventions for alcohol misuse <ul style="list-style-type: none"> Motivation enhancement therapy during detoxification may help to initiate and maintain people in aftercare inpatient treatment programmes compared with treatment as usual plus a peer delivered twelve-step facilitation intervention. Telephone monitoring and counselling may produce better alcohol use outcomes for relapse prevention than telephone counselling and 'treatment as usual'. Using symptom-triggered benzodiazepines in an outpatient setting appears no more effective in reducing alcohol withdrawal symptoms than a fixed dosage regimen, and concerns remain about the safety of high dosage and potential for benzodiazepine misuse in largely unsupervised settings. The cost of treatment for alcohol dependent people after withdrawal may be offset by a reduction in social costs. Quetiapine² does not appear to be effective at reducing alcohol consumption in alcohol dependent people. Baclofen³ does not appear to be effective in the treatment of alcohol withdrawal. Limited evidence suggests that topiramate⁴ may be tolerable at 200 mg in reducing drinking levels in alcohol dependent people. Further research is needed. 		✓ ✓ ✓ ✓ ✓ ✓

²Quetiapine is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

³Baclofen is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

⁴Topiramate is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

Key point	Potential impact on guidance	
	Yes	No
<ul style="list-style-type: none"> Limited evidence suggests that sertraline⁵ may have a short-term treatment effect for relapse prevention on late-onset alcohol dependent people who have the LL (high expression) allele of the 5-HTTLPR serotonin transporter gene polymorphism. Limited evidence suggests that ondansetron⁶ may be effective in maintaining abstinence in alcohol dependent people who have LL or TT alleles of the 5-HTTLPR and rs1042173 serotonin transporter gene polymorphisms. Evidence of the effect of gamma-hydroxybutyrate in alcohol withdrawal is insufficient and concerns exist about its potential for dependence and misuse. Psychological programmes may be effective for patients with alcohol misuse and psychiatric comorbidity. Limited evidence suggests that antidepressants may be effective for the treatment of depression in patients who have comorbid alcohol use disorders. However, some selective serotonin reuptake inhibitors may not be effective. Further research is needed. 		<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓

⁵ Sertraline is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

⁶ Ondansetron is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Principles of care

Working with and supporting families

When the needs of families and carers who are involved in supporting a person who misuses alcohol have been identified, [NICE CG115](#) recommends offering guided self-help and facilitating contact with support groups. If problems continue, the guideline states that family meetings should be considered which may include help in identifying sources of stress related to alcohol misuse and the exploration and promotion of effective coping behaviours.

A systematic review by [Templeton et al. \(2010\)](#) examined psychological interventions for families affected by alcohol misuse. The review included 34 studies (12 randomised controlled trials [RCTs]) with the remainder of differing designs. About half of the studies were from the USA and consisted of approximately 2700 family members (mainly white, adult, female spouses or partners). Studies were included that assessed at least 1 outcome (physical, psychological or 'other', such as family functioning, relationships or use of health or social care services). They had with a psychological component that was directly relevant for family members and was measured at baseline and at least 1 follow-up. The heterogeneity of the studies prevented a quantitative or meta-analysis, so a thematic and narrative approach was used. The studies were divided into 2 groups depending on whether or not the intervention involved the person misusing alcohol. The first group of 21 studies (family members without the person misusing alcohol; n=1500) involved individual or group-oriented interventions. The second group of 13 studies (family members along with the person misusing alcohol; n=1200) involved mainly couples and family-focused approaches.

In the first group (without the person misusing alcohol), 15 of the studies involved mainly female partners or spouses, of which 9 evaluated individual treatment, 3 assessed group treatments, and 3 compared individual with group treatment. Most studies lacked long-term follow-up and a wide range of outcomes were considered, making a summary of quantitative findings difficult. However, collectively the studies indicated that interventions targeting family members' own needs can result in positive change in many areas such as health, coping, stress or distress, hardship and satisfaction (life or relationship). Although treatment groups generally fared better than control groups there was no single intervention that stood out. The remaining 6 studies in the first group focused on children and in general reported the benefits of their interventions.

The second group (involving the person misusing alcohol) consisted of 9 studies using couples therapy, primarily behavioural couples therapy. The authors stated that most studies were well conducted, pragmatic and quantitative trials, and that together the study conclusions indicated that couples therapy resulted in positive outcomes, especially in drinking behaviour and marital adjustment. The other 4 studies in this group were of small-scale holistic family interventions in the UK. All studies indicated that using a therapeutic approach, which closely considers how individual and family resilience can be improved, can positively influence the success of the intervention.

Limitations of the studies were that although a wide range of outcome measures were considered across all studies, often a narrow range of outcomes were considered within studies. These outcomes usually related to the alcohol consumption of the person misusing alcohol or marital functioning. Studies often recruited more white, female participants as partners or spouses. The presentation of outcomes was often misleading with interpretation directed toward the person misusing alcohol rather than the family members. Studies tended to lack detail in many of the same areas: ethics, detail of randomisation, sample size justification, presentation of data and description of outcomes. The length of the follow-up was also short, with only a few studies lasting longer than 2 years.

The evidence from this review is consistent with the recommendations in [NICE CG115](#). The authors suggest that more research is needed to improve outcomes specific to family members and a wider range of family members. As the review focused on primary outcomes related to alcohol misuse the authors suggested a more detailed comparison with other substance misuse would also be useful.

Key reference

Templeton L, Velleman R, Russell C (2010) [Psychological interventions with families of alcohol misusers: a systematic review](#). *Addiction Research and Theory* 18: 616–48

1.2 [Identification and assessment](#)

No new key evidence was found for this section.

1.3 [Interventions for alcohol misuse](#)

Behavioural Interventions

[NICE CG115](#) recommends that for all people who misuse alcohol, a motivational intervention should be carried out as part of the initial assessment. The intervention should contain the key elements of motivational interviewing including: helping people to recognise problems or potential problems related to their drinking, helping to resolve ambivalence and encourage positive change and belief in the ability to change, and adopting a persuasive and supportive rather than an argumentative and confrontational position.

A prospective open-label RCT reported by [Blondell et al. \(2011\)](#) compared treatment as usual (TAU), a motivation enhancement therapy (MET) and a peer-delivered twelve-step facilitation (P-TSF) intervention (n=46 in each arm) to evaluate if a behavioural intervention during alcohol detoxification would facilitate initiation of subsequent care. Participants had all been hospitalised for the medical management of alcohol withdrawal, and were excluded if they were unable to give informed consent, were enrolled in a methadone programme, or were homeless. The primary outcome was the initiation of mutual self-help meeting attendance, or professional out-patient counselling, or an admission to either an inpatient or a residential rehabilitation facility within 30 days of hospital discharge. Secondary 90-day outcomes included initiation of treatment services; number of mutual self-help meetings attended; and self-reported drinking behaviours.

The TAU group (the active comparator control) received 1-hour group therapy sessions twice daily. Individual counselling sessions, family sessions, and self-help meetings were available, but attendance was not obligatory. A benzodiazepine was typically used to manage alcohol withdrawal and typical length of stay was 3–5 days. The MET group received TAU and an individual 5–60 minute motivational interview based on a standard protocol. Compared with TAU, the MET intervention placed more emphasis on obtaining specific commitments for aftercare and relapse plans. The P-TSF group received TAU and a 45–60 minute visit by volunteers who were recovering from alcoholism, and were also given information and meeting schedules for Alcoholic Anonymous meetings.

At 30-day follow-up, 74–82% of the participants in each group had begun some form of professional rehabilitation treatment and 65–66% had attended at least 1 meeting of a mutual self-help group; however across the 3 groups there was no significant difference in the rates for the initiation of any kind of rehabilitation service. At 90-day follow-up, initiation of inpatient rehabilitation after hospitalisation was lower among those assigned to P-TSF (31%) and TAU (45%) compared with the MET group (61%, $p=0.025$). Completion of inpatient treatment was also lower in the P-TSF (23%) and TAU (36%) groups compared with the MET group (51%, $p=0.033$). However, there were no significant differences in relapse to drinking (49–55%) at 90 days across all 3 groups, but participants in the P-TSF group relapsed to drug use before the other 2 groups ($p=0.003$). In all groups, the mean number of drinking days was below 18 and the proportion of days without drinking was above 80%.

A limitation of the study was that there was no information on the extent of participants' drinking at baseline. Other limitations noted by the authors were that the study only included participants who could provide their own consent and excluded homeless people (a potentially high-risk population), which may explain the favourable outcomes. The authors also noted that the services provided by TAU were extensive and the additional benefits of brief intervention may be negligible. This was a small study and interventions may have been effective but the study was underpowered to detect an effect. In addition, some patients receiving treatment for alcohol withdrawal show memory problems and so may not have recalled the intervention. The extent of their alcohol dependence could also have limited the effectiveness of the intervention.

This study was undertaken in the USA and details intensive interventions that may not be available in the UK unless the service user is a heavy drinker or has specific medical or psychiatric needs. While there were no differences in drinking-related outcomes, MET appeared to provide benefits in term of initiating and maintaining patients in aftercare inpatient treatment programmes. The results of this study are also consistent with the recommendations in [NICE CG115](#) for the inclusion of motivational interviewing and are unlikely to have an impact on the guidance.

Key reference

Blondell RD, Frydrych LM, Jaanimagi U et al. (2011) [A randomized trial of two behavioral interventions to improve outcomes following inpatient detoxification for alcohol dependence](#). *Journal of Addictive Diseases* 30: 136–48 [[NIH Public Access author manuscript – full text](#)]

Telephone continuing care

[NICE CG115](#) recommends considering case management to increase engagement in treatment for people who have moderate to severe alcohol dependence and who are considered at risk of dropping out of treatment or who have a previous history of poor engagement. If case management is provided it should be throughout the whole period of care, including aftercare. For harmful drinkers and people with mild alcohol dependence [NICE CG115](#) recommends offering a psychological intervention, such as cognitive behavioural therapies (CBTs), behavioural therapies or social network and environment-based therapies, focused specifically on alcohol-related cognitions, behaviour, problems and social networks.

A substudy of an RCT by [Lynch et al. \(2012\)](#) evaluated potential moderators of the effect of adding telephone monitoring (TM, $n=83$) or telephone monitoring and counselling (TMC, $n=83$) to treatment as usual (TAU, $n=86$) for the treatment of alcohol dependence. TAU consisted of up to 4 months of intensive outpatient programmes (IOP) providing about 9 hours of group-based treatment per week, but without any telephone continuing care. TM consisted of a brief assessment of current symptom severity and functioning plus feedback, without any counselling. Calls of 5–10 minutes were offered weekly for the first 8 weeks, every other week for the next 44 weeks, and once per month for the last 6 months. TMC followed the same schedule as TM, but the intervention also featured CBT techniques. Patients were recruited

after they had completed 3–4 weeks of treatment in the IOP and were then evaluated at 3, 6, 9, 12, 15 and 18 months. Participants were alcohol dependent, determined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and were excluded if they were heroin users or homeless. Most participants were male (64.3%), African-American (88.9%), not married (91.3%), and met criteria for current alcohol dependence in the 30 days prior to entering treatment (79.7%) with 49.2% also having current cocaine dependence.

Effectiveness results of the RCT were previously reported by [McKay et al. \(2011\)](#) and indicated that the best alcohol-use outcomes were in TMC. For proportion of days of alcohol use, TMC resulted in less frequent drinking than TAU at 12 months ($p < 0.02$), 15 months ($p = 0.0002$) and 18 months ($p = 0.004$) and less frequent drinking than TM at 6 months ($p = 0.02$). TM produced less frequent drinking than TAU at 12 and 15 months ($p = 0.03$). Rates of drinking were lower in the TMC than the TAU group across each follow-up period ($p = 0.02$), but there were no differences between TM and TAU ($p = 0.42$).

The study by Lynch et al. (2012) assessed whether the main effect results were moderated by factors assessed at intake to treatment and whether certain types of patients were likely to benefit from a particular intervention. The 11 moderator variables were: years of regular alcohol use, years of heavy alcohol use, number of prior treatments for alcohol problems, days of alcohol use, heavy alcohol use, cocaine use during IOP, craving levels, motivation for change, self-efficacy, perceptions about harm of continued substance misuse and potential benefits of treatment, and gender. None of the variables interacted significantly with treatment type to predict frequency of alcohol use over the 18-month follow-up (all interactions $p \geq 0.16$, with all but 2 interactions $p > 0.6$). There was also no prediction of alcohol use versus abstinence over the 18-month follow-up (1 interaction $p = 0.11$, all others $p > 0.6$). However, there were significant moderation effects favouring TM over TAU in readiness for change ($p = 0.04$). Lower motivation predicted more frequent alcohol use in TAU ($p = 0.02$). In women, TM produced a lower likelihood of any alcohol use compared with TAU ($p = 0.006$). TM produced better outcomes in those with low readiness for change ($p = 0.06$), but worse outcomes for those with high readiness for change ($p = 0.05$).

Limitations of the study cited by the authors included that about three quarters of participants who were screened for the study were excluded and these participants may have been the ones most in need of extended monitoring and support. Also, collateral reports obtained on alcohol use were only available for less than 50% of participants so there was no substantiation for the remainder of self-reports.

The results of this study suggest that although TMC produced the best alcohol use outcomes there were no moderators that interacted significantly with treatment type. This study is unlikely to have an effect on [NICE CG115](#) as long-term case management is already offered as an option throughout care and aftercare. While TMC is not suggested in the guidance, CBT is recommended as an option for psychological intervention. However, there is no recommendation over whether it should be delivered face-to-face or by telephone. The authors indicated that the results of this study should be considered as exploratory and in need of confirmation from further research.

Key reference

Lynch KG, Van Horn D, Drapkin M et al. (2010) [Moderators of response to telephone continuing care for alcoholism](#). *American Journal of Health Behavior* 34: 788–800 [\[NIH Public Access author manuscript – full text\]](#)

Supporting reference

McKay JR, Van Horn D, Oslin D et al. (2011) [Extended telephone-based continuing care for alcohol dependence: 24 month outcomes and subgroup analyses](#). *Addiction* 106: 1760–9 [\[NIH Public Access author manuscript – full text\]](#)

Dosing regimens for alcohol withdrawal

When conducting community-based assisted withdrawal programmes, [NICE CG115](#) recommends using fixed-dose medication regimens, defined as starting with a standard dose, determined by the level of alcohol dependence, and reducing the dose to zero over 7–10 days according to a standard protocol. In a community-based assisted withdrawal programme, the service user should be monitored every other day during assisted withdrawal. A family member or carer should preferably oversee the administration of medication and adjust the dose if severe withdrawal symptoms or over-sedation occur. The [full version of CG115](#) states that doses of chlordiazepoxide prescribed for hospital inpatients in excess of 30 mg 4 times a day should only be prescribed in cases where severe withdrawal symptoms are expected and the patient's response to the treatment should always be regularly and closely monitored. Doses in excess of 40 mg 4 times a day should only be prescribed where there is clear evidence of very severe alcohol dependence.

An RCT by [Elholm et al. \(2011\)](#) assessing the use of chlordiazepoxide (a benzodiazepine) in 165 alcohol-dependent patients undergoing alcohol withdrawal was previously discussed in [NICE Evidence Update 10 'Alcohol-use disorders: physical complications' \(2012\)](#) which gives a full overview of the trial. Briefly, the trial compared an out-patient symptom-triggered regimen with a fixed-dose regimen. People took one of two regimens depending on the severity of their withdrawal. In the fixed-dose group people received 200 mg/day tapering to 25 mg/day or 80 mg/day tapering to 10 mg/day. In the symptom-triggered group, people were prescribed a maximum daily dose of 300 mg for 10 days or a maximum daily dose of 120 mg. The authors found no difference in treatment effectiveness between the two regimens.

Limitations of the study include the high proportion of patients living alone (49% in the symptom-triggered group and 30% in the fixed-schedule group, $p < 0.05$), and daily doses of chlordiazepoxide much higher than those recommended by current guidance. There was also an opportunity to take additional medication according to symptoms and patients were not closely monitored.

This study suggests that the use of a symptom-triggered regimen for assisted alcohol withdrawal in the outpatient setting has no advantage over a fixed-dose regimen and it may also compromise patient safety. Because of the limitations of the study it is unlikely to have an impact on the recommendations of [NICE CG115](#).

Key reference

[Elholm B, Laursen K, Hornnes N et al. \(2011\) Alcohol withdrawal syndrome: symptom-triggered versus fixed-schedule treatment in an out-patient setting. Alcohol and alcoholism 46: 318–23](#)

Social costs of alcohol dependence

[NICE CG115](#) recommends that, after a successful withdrawal, clinicians should consider offering people with moderate and severe alcohol dependence acamprosate or oral naltrexone in combination with an individual psychological intervention (CBT, behavioural therapy or social network and environment-based therapy) focused specifically on alcohol misuse. At the time of publication of this Evidence Update, oral naltrexone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

The Combined Pharmacotherapies and Behavioural Intervention (COMBINE) RCT examined whether combinations of pharmacotherapies (acamprosate and naltrexone) and behavioural therapies (medical management [MM] and combined behavioural intervention [CBI]) were better than monotherapies in treating alcohol dependence. Participants were randomised into 9 treatment groups. Eight of the groups (all MM) formed a 2x2x2 factorial design, where patients were randomised to receive acamprosate (active or placebo), naltrexone (active or

placebo), and either CBI or no additional behavioural therapy. The ninth group received only CBI. The effectiveness results of this trial were previously reported by [Anton et al. \(2006\)](#).

This study by [Zarkin et al. \(2010\)](#) evaluated broader social outcomes and costs over 3 years (n=786). The social costs utilised were the sum of treatment costs and the economic costs of healthcare utilisation, arrests, and motor vehicle accidents. The costs of treatment are those reported in the COMBINE cost-effectiveness analysis by [Zarkin et al. \(2008\)](#) and include pharmaceutical, labour, and laboratory and non-laboratory assessment costs for delivering the 9 COMBINE treatments over 16 weeks. The mean cost across all treatment groups 3 years post-randomisation was \$13,965, the median cost was \$5861, and the 90th percentile was \$34,391. Healthcare costs accounted for 52% of total costs, and motor vehicle costs were 33% of total costs. Arrest costs were 7.9% of total costs, and COMBINE treatment costs were 6.3% of total costs. MM plus acamprosate plus naltrexone had the lowest mean cost (\$11,742) and MM plus acamprosate had the lowest median cost (\$4639). CBI had the largest mean cost (\$14,938), and MM plus placebo had the largest median cost (\$8637). Healthcare, arrest, and motor vehicle accident costs were skewed by the large values for the 90th percentile, such as motor vehicle costs (\$14,576 for 1 car accident).

There were no significant differences in mean costs between any of the treatment arms as compared with MM plus placebo at 3 years. This may be because of the skewed data caused by rare, but expensive inpatient hospital stays, arrests, and motor vehicle accidents. By using median costs the results are less affected by high cost outliers. At 3 years, median costs of MM plus acamprosate, MM plus naltrexone, MM plus acamprosate plus naltrexone, and MM plus acamprosate plus CBI were significantly lower than the median cost for MM plus placebo. Median cost differences ranged from \$2500 to \$3800 less than the median costs of MM and placebo.

The authors stated there were a number of limitations to their study. Their analysis examined only a subset of possible social costs and they did not examine labour market outcomes because of the difficulty of costing these. They used peer-reviewed literature for their cost estimates and used their own judgement in which unit costs to include. All treatment groups were compared with MM plus placebo, however MM plays an important treatment role. They recognised that expensive rare events, such as motor vehicle accidents may greatly affect mean costs, especially with their sample size.

This study is from the USA and so the utilised costs may not be directly relevant to the UK. However, this study demonstrates the reduction in social costs achieved through the use of alcohol treatment in alcohol dependent people and is consistent with [NICE CG115](#).

Key reference

[Zarkin GA, Bray JW and Aldridge A et al. \(2010\) The effect of alcohol treatment on social costs of alcohol dependence: results from the COMBINE study. Medical Care 48: 396–401 \[NIH Public Access author manuscript – full text\]](#)

Supporting references

[Anton RF, O'Malley SS, Ciraulo DA, et al. for the COMBINE Study Research Group \(2006\) Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE Study: a randomized controlled trial. Journal of the American Medical Association 295: 2003–17](#)

[Zarkin GA, Bray JW, Aldridge A et al. for the COMBINE Cost-Effectiveness Research Group \(2008\) Cost and cost-effectiveness of the COMBINE study in alcohol-dependent patients. Archives of General Psychiatry 65: 1214–21](#)

Quetiapine

Quetiapine is not recommended by [NICE CG115](#) for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

A multicentre, placebo-controlled, double-blind RCT (n=218) by [Litten et al. \(2012\)](#) compared quetiapine with placebo in alcohol dependent patients. Participants were alcohol dependent, determined by DSM-IV, who had drunk very heavily (at least 8 drinks per drinking day for women or 10 drinks for men, on at least 40% of the days before the screening visit). They were without dependence on psychoactive substances other than alcohol and nicotine. All participants received up to 9 sessions of medical management (a psychosocial, medically based, minimally intensive intervention). The primary outcome measure was weekly proportion of heavy-drinking days during study weeks 3–11. Secondary outcome measures included other drinking measures as well as non-drinking outcomes.

There were no statistically significant differences in the unadjusted mean proportion of heavy drinking days between groups (all $p > 0.41$) in weeks 3–11. Further analysis using a fully adjusted mixed model across weeks 3–11 also failed to show a difference between groups for this outcome ($p = 0.68$), or any of the 7 secondary drinking outcomes (p values ranged from 0.144 to 0.972). Similarly, the model also showed no difference between groups on several non-drinking outcomes including alcohol related consequences ($p = 0.42$), alcohol craving ($p = 0.363$), and anxiety ($p = 0.371$). However, greater improvements with quetiapine versus placebo were seen during the course of the study for both depression ($p = 0.011$) and sleep quality ($p = 0.009$). Adverse events occurring in at least 10% of patients in the quetiapine group were all more frequently observed in the treatment group compared with placebo: dizziness ($p = 0.017$), dry mouth ($p < 0.0001$), dyspepsia ($p = 0.001$), increased appetite ($p = 0.001$), sedation ($p = 0.001$), and somnolence ($p < 0.001$).

A limitation of the small study was that it was underpowered to detect a treatment effect. The authors also stated that the high functionality and lack of psychiatric symptoms of the study population mean that larger treatment effects may be found in participants with more problems in these areas. Consequently, they recommended that future studies test the efficacy of quetiapine in comorbid alcohol-dependent populations.

The results of this study found no significant difference between quetiapine and placebo in reducing alcohol consumption in alcohol-dependent patients and so they are unlikely to have an impact on [NICE CG115](#).

Key reference

Litten RZ, Fertig JB, Falk DE et al. [A double-blind placebo controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients](#). *Alcoholism: Clinical and Experimental Research* 36: 406–16

Baclofen

Baclofen is not recommended by [NICE CG115](#) for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

A double-blind, placebo controlled RCT (n=80) by [Garbutt et al. \(2010\)](#) compared baclofen with placebo over 12 weeks of treatment. Participants had to meet DSM-IV criteria for current alcohol dependence, have at least 2 heavy drinking days per week (defined as at least 4 standard drinks per day for women and at least 5 drinks for men) on average during the 4 weeks prior to screening, and had to refrain from alcohol for 3 days prior to randomisation. Patients were excluded if they had any clinically significant psychiatric illness. Primary outcome measures were the proportion of heavy drinking days and the percentage of days

abstinent. Secondary outcomes included effect of treatment on cravings, anxiety and depression. Participants were randomised to 30 mg per day baclofen or placebo. All participants took part in 8 sessions of a biopsychosocial therapy (BRENDA).

Although the proportion of heavy drinking days decreased in both groups over time ($p < 0.001$), there was no significant difference during treatment between average rates of heavy drinking with baclofen (25.5%, $SD = 23.6\%$) or placebo (25.9%, $SD = 23.2\%$, between-group difference $p = 0.56$). There was also no significant effect with baclofen on the proportion of abstinent days ($p = 0.50$). General mixed model results indicated no significant differences between baclofen and placebo for craving ($p = 0.13$), depression ($p = 0.10$) or anxiety ($p = 0.14$). However, the average severity of anxiety was significantly less with baclofen (32.2, $SD = 16.7$) than placebo (27.5, $SD = 13.5$; $p = 0.02$), as determined by the Spielberger Trait and State Anxiety Inventory.

No significant differences between baclofen and placebo were found for time to first use of alcohol ($HR = 0.70$, $p = 0.13$) and first heavy use ($HR = 0.92$, $p = 0.76$); however the confidence intervals were not reported. There was also no difference in effect between genders. Only 2 adverse events affected more than 5% of the sample, drowsiness (placebo=10%, baclofen=28%, $p = 0.08$) and headaches (placebo=10%, baclofen=3%, $p = 0.36$).

A limitation of this small study was that it was not reported whether the study was sufficiently powered to detect an effect. The authors also stated that this isolated study should be viewed with caution as further research is needed to confirm these findings.

The results of this study found no significant difference between baclofen and placebo on alcohol consumption and related harm in patients with alcohol dependence. Therefore, it is unlikely to have an impact on [NICE CG115](#).

Key reference

Garbutt JC, Kampov-Polevoy AB, Gallop R et al. (2010) [Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial](#). *Alcoholism: Clinical and Experimental Research* 34: 849–57 [[NIH Public Access author manuscript – full text](#)]

Topiramate

Topiramate is not recommended by [NICE CG115](#) for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

At the time of publication of this Evidence Update oral naltrexone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

An unblinded, randomised naturalistic trial (observing and recording patients in the community) by [Florez et al. \(2011\)](#) evaluated the tolerability and effectiveness of topiramate ($n = 91$) compared with naltrexone ($n = 91$). Participants had to meet criteria for alcohol dependence and have an ethanol intake, during the past 6 months, of at least 210 g/week for men and 140 g/week for women. Participants with dependence on all other substances except nicotine were excluded. All participants were detoxified before starting treatment. Patients were randomised to 6 months of treatment with naltrexone (set dose of 50 mg per day), or topiramate (starting dose of 50 mg per day rising by 50 mg every week to a maximum dose of 200 mg per day). All patients received weekly biopsychosocial therapy (BRENDA). The primary outcome measure was a composite score from rating scales evaluating levels of abstinence, moderate drinking without problems, moderate drinking with problems, and heavy drinking with or without problems.

At 6 months, there were no significant differences between topiramate and naltrexone for abstinence (47.3% vs 41.8%, $p = 0.650$), percentage days abstinent (66.40% vs 62.31%, $p = 0.566$), or total drinking days (30.35% vs 33.94%, $p = 0.579$). However, in the topiramate group there was significantly more moderate drinking without problems (74.8% vs 51.7%,

p=0.003), significantly fewer drinks per drinking day (1.41 drinks vs 2.3 drinks, p=0.013), and significantly fewer heavy drinking days (3.35% vs 8.65%, p=0.021). At 3 months patients taking topiramate reported more adverse events than those taking naltrexone (19.78% vs 5.49%, p=0.004). These differences disappeared at the 6 month evaluation (4.3% vs 1.5%, p=0.088).

The authors stated a number of limitations. There was no blinding and no placebo group. In addition, the treatment group had a good prognosis for this type of trial (no physical or mental illness, not living alone and not dependent on other drugs). The 6-month treatment time covered the dishabituation phase, but not the relapse prevention phase, which would need to be monitored over a longer observation period.

This study indicates that topiramate may be tolerable at doses of 200 mg, but there is insufficient evidence to support the efficacy of topiramate over naltrexone. More research is needed so the results of this study are unlikely to have an impact on [NICE CG115](#).

Key reference

Florez G, Saiz PA, Garcia-Portilla P et al. (2011) [Topiramate for the treatment of alcohol dependence: comparison with naltrexone](#). *European Addiction Research* 17: 29–36

Genetic polymorphisms – sertraline

[NICE CG115](#) recommends that antidepressants (including selective serotonin reuptake inhibitors [SSRIs]) should not be used routinely for the treatment of alcohol misuse alone.

Sertraline is not recommended by current guidance for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

A placebo-controlled, double-blind, prospective RCT (n=134) by [Kranzler et al. \(2011\)](#) evaluated the effectiveness of sertraline for the treatment of alcohol dependence over 12 weeks. The authors studied people with alcohol dependence defined as either 'late-onset/low vulnerability' or 'early-onset/high vulnerability' alongside the moderating effects of a functional polymorphism in the serotonin transporter gene. The primary outcome was the number of drinking days and heavy drinking days (defined as at least 4 standard drinks per day for women and at least 5 drinks for men). Participants were genotyped for the triallelic 5-HTTLPR polymorphism and designated as having low expression (S) or high expression (L) alleles. The L_G and S alleles were grouped together as S and the L_A allele designated as L. Patients were randomised to receive up to 200 mg of sertraline or placebo per day and all patients received 9 coping skills training sessions.

In those with the homozygous LL allele, sertraline treatment resulted in significantly fewer drinking and heavy drinking days from pre-treatment levels in the late-onset group (p=0.011), but greater reductions in drinking and heavy drinking days were seen in the early-onset group with placebo (p<0.001). However, no significant treatment effects were seen in those with the S allele.

A post-treatment extension of this study was reported by [Kranzler et al. \(2012\)](#). The sertraline group effect remained significant during the 3-month post-treatment follow-up period for LL allele people with late-onset alcohol dependence, having fewer drinking days than the placebo group (p=0.027). However, the placebo group effect seen in LL allele people with early-onset alcohol dependence during treatment was no longer significant (p=0.48). There were no significant effects among those with S alleles at the 3 month follow-up visit, or in either the LL or S genotype groups at the 6-month follow-up.

The authors stated that the small sample sizes and high rates of attrition mean these findings are preliminary and suggest that further research on larger groups is needed. At present this

type of polymorphism-guided treatment for alcohol dependence is not part of UK practice so these findings are unlikely to have an impact on [NICE CG115](#).

Key references

Kranzler HR, Armeli S, Tennen H et al. (2011) [A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset and 5-HTTLPR genotype](#). *Journal of Clinical Psychopharmacology* 31: 22–30 [[NIH Public Access author manuscript – full text](#)]

Kranzler HR, Armeli S, Tennen H (2012) [Post-treatment outcomes in a double-blind, randomized trial of sertraline for alcohol dependence](#). *Alcoholism: Clinical and Experimental Research* 36: 739–44

Genetic polymorphisms – ondansetron

Ondansetron is not recommended by [NICE CG115](#) for moderate and severe alcohol dependence after successful withdrawal. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

A placebo-controlled, double-blind RCT (n=283) by [Johnson et al. \(2011\)](#), evaluated ondansetron (4 micrograms/kg twice daily) for 11 weeks, plus standardised CBT. Participants were randomised by genotype for the 5-HTTLPR polymorphism and designated as having LL, LS, and SS genotypes. They were then genotyped for another polymorphism from the 5-HTT gene, rs1042173, and designated as having TT, TG, or GG genotypes. Participants with the LL genotype who received ondansetron had fewer drinks per drinking day (mean difference=-1.62, p=0.002) and a greater percentage of days abstinent (mean difference=11.27 percentage points, p=0.013) compared with the placebo group. Among the ondansetron group, those with the LL genotype had fewer drinks per drinking day (mean difference=-1.53, p=0.005) and a greater proportion of days abstinent (mean difference=9.73 percentage points, p=0.03) than LS/SS participants. LL individuals in the ondansetron group also had fewer drinks per drinking day (mean difference=-1.45, p=0.002) and a greater proportion of days abstinent (mean difference=9.65 percentage points, p=0.013) than all other genotype and treatment groups combined. Participants with both the LL and TT genotypes in the ondansetron group had significantly fewer drinks per drinking day (mean difference=-2.63, p=0.0002) and a greater proportion of days abstinent (mean difference=16.99 percentage points, p=0.005) than all the other genotype and treatment groups combined.

These results are unlikely to have an impact on [NICE CG115](#) as successful treatment with ondansetron was limited to participants with a specific allelic construction of the 5-HTT gene and this type of polymorphism-directed treatment is not part of UK practice at the present time.

Key reference

Johnson BA, Ait-Daoud N, Seneviratne C. et al. (2011) [Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking](#). *American Journal of Psychiatry* 168: 265–75

Gamma-hydroxybutyrate

[NICE CG115](#) recommends that gamma-hydroxybutyrate (GHB) should not be used for the treatment of alcohol misuse. At the time of publication of this Evidence Update it did not have UK marketing authorisation for this indication.

A Cochrane review of gamma-hydroxybutyrate (GHB) in alcohol withdrawal by [Leone et al. \(2010\)](#) was previously discussed in [NICE Evidence Update 10 'Alcohol-use disorders: physical complications' \(2012\)](#). The commentary concluded that evidence is insufficient to be confident of a difference in efficacy between GHB and placebo or whether GHB is more or less effective than other drugs. It also highlighted the concerns about dependence and risk of misuse or abuse of GHB. These findings are consistent with the recommendations in [NICE CG115](#), which states 'do not use GHB for the treatment of alcohol misuse'.

Key reference

Leone MA, Vigna-Taglianti F, Avanzi G et al. (2010) [Gamma-hydroxybutyrate \(GHB\) for treatment of alcohol withdrawal and prevention of relapses](#). Cochrane Database of Systematic Reviews issue 2: CD006266.

Comorbid mental health disorders – psychological therapy

[NICE CG115](#) recommends psychological interventions for all people who misuse alcohol including carrying out a motivational intervention as part of an initial assessment. For harmful drinkers and people with mild alcohol dependence, the guidance recommends offering a psychological intervention (such as cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol-related cognitions, behaviour, problems and social networks. For people who misuse alcohol and have comorbid depression or anxiety disorders, [NICE CG115](#) recommends treating the alcohol misuse first as this may lead to significant improvement in the depression and anxiety. If, however, depression or anxiety continues after 3 or 4 weeks of abstinence from alcohol, the depression or anxiety should be assessed and referral and treatment in line with the relevant NICE guideline for that particular disorder should be considered.

A systematic review by [Baker et al. \(2012\)](#) evaluated whether psychological interventions that target alcohol misuse among people with co-occurring depressive or anxiety disorders were effective. Eight RCTs (n=831) were identified including people with comorbid depression (2 trials), dysthymia (1 trial), inpatients with mixed diagnoses (2 trials), social phobia (1 trial), social phobia or agoraphobia (1 trial), agoraphobia or panic disorder (1 trial). The authors stated that meta-analysis was inappropriate due to considerable heterogeneity in clinical characteristics of participants and type of treatment and outcome measures used.

For studies assessing psychological interventions, 2 studies suggested that coexisting depression and alcohol misuse were responsive to psychological treatment, including brief integrated motivational intervention (MI) and up to 10 sessions of CBT. Both studies also suggested that stepped care was worth further investigation. For longer interventions, CBT appeared to be suitable for men and women (1 study) delivered by therapist or computer (1 study), individual (1 study) and group (1 study). MI among psychiatric hospital inpatients, primarily with depression, was effective in reducing alcohol at follow-up (1 study), but results were modest and replication is needed.

For alcohol misuse and anxiety disorders, psychological intervention reduced both anxiety and alcohol consumption, including brief behavioural interventions focusing on alcohol (1 study). Two of 3 studies suggested further research on a stepped care approach is needed.

This review focused on a mixed group of participants and none of the studies were completed on a UK population. The authors' most commonly identified limitations of the studies were: failure to obtain more than 85% of subjects initially allocated to groups at follow-up (4 studies), lack of intention-to-treat analysis (3 studies), lack of clarity regarding concealment of allocation (3 studies), dissimilar baseline characteristics (3 studies), short-term follow-up studies (4 studies), recruitment of heterogeneous samples with different mental disorders (3 studies), reliance on self-reported alcohol consumption (3 studies), and small sample sizes (2 studies).

The results of this review are broadly consistent with [NICE CG115](#) that psychological programmes (motivational interviewing and cognitive behavioural interventions) are effective for people with alcohol misuse or dependence so this evidence is unlikely to have an impact on guidance. The authors do, however, provide a number of recommendations for further research.

Further advice on the treatment of depression in this population can be found in 'Depression: the treatment and management of depression in adults' ([NICE CG90](#)). Further advice on the

treatment of anxiety in this population can be found in 'Generalised anxiety disorder and panic disorder: with or without agoraphobia in adults' ([NICE CG113](#)).

Key reference

Baker AL, Thornton LK, Hiles S et al. (2012) [Psychological interventions for alcohol misuse among people with co-occurring depression or anxiety disorders: A systematic review](#). *Journal of Affective Disorders* 139: 217–29

Comorbid mental health disorders – antidepressant therapy

[NICE CG115](#) recommends that antidepressants (including selective serotonin reuptake inhibitors [SSRIs]) should not be used routinely for the treatment of alcohol misuse alone.

A meta-analysis by [Iovieno et al. \(2011\)](#) examined 11 randomised, double-blind, placebo-controlled studies (n=891) of single-therapy oral antidepressant use in patients with unipolar depression (major depressive disorder and dysthymic disorder) with comorbid alcohol use disorders. Clinical response was defined as a 50% or greater reduction in Hamilton Depression Rating Scale or Montgomery-Asberg Depression Rating scale scores, from baseline to endpoint, or a Clinical Global Impressions-Improvement of Illness Scale score of less than 3 at the final visit.

The pooled response rate of 57.8% with antidepressants was significantly higher than the 47.1% response rate seen with placebo (risk ratio [RR]=1.34, 95% CI 1.05–1.71, p=0.021). However, when studies involving selective serotonin reuptake inhibitors (SSRI) only were considered, the difference in response rates with antidepressants (59.3%) versus placebo (53.1%) were not significant (RR=1.16, 95% CI 0.90–1.50, p=0.263). There was also no significant difference in response to antidepressants between trials that specified a minimum period of abstinence versus those including patients who were actively drinking (p=0.915). Baseline severity of drinking did not predict a significant difference in response rate to antidepressants (p=0.467). In a post hoc meta-analysis of 2 studies, there was no significant difference in the percentage of heavy drinking days with antidepressants versus placebo (RR=0.69, 95% CI 0.36–1.34, p=0.275).

There were a number of limitations to the meta-analysis. The majority of evidence supporting antidepressants was derived from studies that evaluated older tricyclic antidepressants and there was a complete lack of data on a number of the newer antidepressants. The authors stated that there was a paucity of data on patients with unipolar depression with comorbid alcohol use disorders and the follow-up duration was short. They also stated that publication bias may be an issue as published studies may offer more unequivocal results than unpublished studies, which were not included. Pooling of trial results with different inclusion and exclusion criteria may also exclude a number of patient groups from analysis. The authors did attempt to include mostly alcohol dependent patients defined by DSM criteria, but some patients with alcohol misuse rather than alcohol dependence were included in the analyses.

The meta-analysis concluded that antidepressants are effective in the treatment of depression in patients who have comorbid alcohol use disorders. However, many of the studies evaluated were not from the UK and patients meeting alcohol-use disorder criteria may have been less dependent than those typically seeking treatment in the UK. Due to the limitations discussed, this evidence is unlikely to have an impact on [NICE CG115](#). Further research is needed on the effectiveness of antidepressants in patients with comorbid alcohol use disorders.

Key reference

Iovieno N, Tedeschini E, Bentley KH et al. (2011) [Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials](#). *Journal of Clinical Psychiatry* 72: 1144–51

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Principles of care

- [Interventions with families of alcohol misusers](#)

Interventions for alcohol misuse

- [Topiramate for the treatment of alcohol dependence](#)

Further evidence uncertainties for alcohol use disorders: harmful drinking and alcohol dependence can be found in the [UK DUETs database](#) and in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Alcohol-use disorders: harmful drinking and alcohol dependence](#). NICE clinical guideline 115 (2011).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 March 2010 (the end of the search period of NICE Clinical Guideline 115) to 8 August 2012:

- AMED (Allied and Complementary Medicine Database)
- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs and systematic reviews](#).

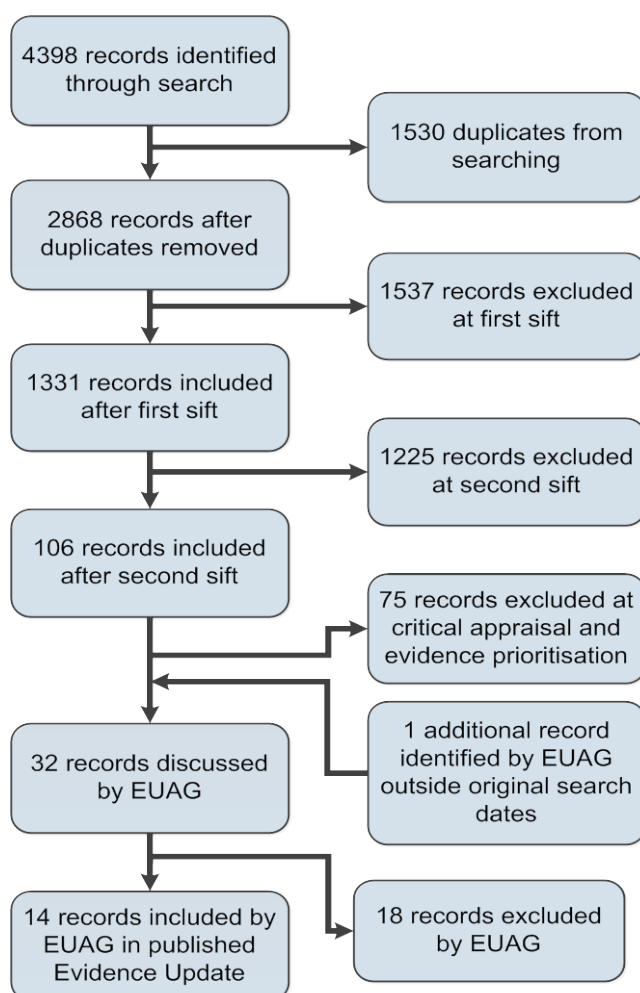
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about [how NICE Evidence Updates are developed](#) on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Alcoholism/ or exp Alcohol, Amnestic disorder/ or Psychoses, alcoholic/ or (alcohol-related disorders or alcohol-induced disorders or sobriety).sh.		hazard\$ or heavy or high risk or intoxicat\$ or misus\$ or overdos\$ or (over adj dos\$) or problem\$ or rehab\$ or reliance or reliant or relaps\$ or withdraw\$)).ti,ab.
2	(alcoholi\$ or (alcohol\$ and (abstinence or detoxification or intoxicat\$ or rehabilit\$ or withdraw\$))).hw.	5	(control\$ adj2 drink\$).tw.
3	alcoholi\$.ti,ab.	6	sobriet\$.ti,ab,hw.
4	(drinker\$1 or (drink\$ adj2 use\$1) or ((alcohol\$ or drink\$) adj5 (abstinen\$ or abstain\$ or abus\$ or addict\$ or attenuat\$ or binge\$ or crav\$ or dependen\$ or detox\$ or disease\$ or disorder\$ or excessiv\$ or harm\$ or	7	1 or 2 or 3 or 4 or 5 or 6

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group



Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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