NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review consultation document

4-year surveillance review of:

CG100: Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications

CG115: Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence

Background information CG100

Guideline issue date: June 2010
4 year review: 2015

Background information CG115

Guideline issue date: February 2011
4 year review: 2015

Surveillance review recommendation

Surveillance review proposal for consultation:

The Alcohol–use disorder guidelines, CG100 and CG115, should not be considered for an update at this time.

Main findings of the current 4 year surveillance review

Evidence Updates were produced for the guidelines, CG100: EU10 in 2012 and CG115: EU28 in 2013 which were used as a source of evidence for the review proposal. The Evidence Updates did not indicate that there was new evidence to generate future change in either guideline.

A literature search was conducted for randomised controlled trials (RCTs) and systematic reviews from the end of the search period for each Evidence Update to 11th November 2014 and relevant abstracts were assessed. Clinical feedback was also obtained from members of the guideline development groups (GDG) through a questionnaire. All studies highlighted through the GDG questionnaire that were relevant to the scope of the guideline and met the study type inclusion criteria have been summarised in the evidence summary section of the table.

NICE guideline on alcohol-use disorders (clinical management) (CG100)

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the NICE guideline on alcohol-use disorders (clinical management). This guideline covers inpatient unplanned alcohol withdrawal, alcohol related pancreatitis and alcohol related hepatitis.

Clinical Area 1. Acute Alcohol Withdrawal		
Q: What is the safety and efficacy of a benzodiazepine (chlordiazepoxide or diazepam, alprazolam, oxazepam, clobazam, lorazepam) versus a) placebo b) other benzodiazepines (chlordiazepoxide or diazepam, alprazolam, oxazepam, clobazam, lorazepam) c) other agents (clomethiazole or carbamazepine) d) other agents (clomethiazole or carbamazepine) versus placebo for patients in acute alcohol withdrawal?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) **Benzodiazepines** A Cochrane review (including 64 studies, n=4309) of participants undergoing alcohol withdrawal found that for reduction in seizures, benzodiazepines were more effective than placebo[1]. However, benzodiazepines did not show a benefit compared with other drugs. **Anticonvulsants** A second Cochrane review (including 56 studies, n=4076) for alcohol withdrawal indicated	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** **Benzodiazepines** The updated Cochrane review identified by the Evidence Update and the trial from the 4 year surveillance review support the current recommendations in NICE CG100 for the use of benzodiazepines for acute alcohol withdrawal. **Anticonvulsant** The results for both the Evidence Update and RCT identified at the 4 year surveillance review support NICE CG100, which recommends carbamazepine

anticonvulsants were not effective for reducing alcohol withdrawal seizures, adverse events, drop-outs or drop-outs due to adverse events compared to placebo[2]. However, carbamazepine was more effective than benzodiazepines in reducing the Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) score at the end of treatment. **Muscle relaxants** A Cochrane review examining baclofen for alcohol withdrawal identified only 1 study (n=37) that met the inclusion criteria[3]. The study showed that baclofen and diazepam both reduced CIWA–Ar scores with no differences between treatments, although baclofen took longer to work. <u>4-year surveillance review (2015)</u> **Benzodiazepines** Lorazepam was found to be more effective in terms of a faster response rate in the drop of withdrawal severity and total duration of withdrawal compared to chlordiazepoxide in a RCT in people undergoing alcohol withdrawal(n=108)[4]. **Anticonvulsants** A RCT on the efficacy and safety of 6 day treatment with fixed dose pregabalin (not licensed for this indication) for attenuating the severity of alcohol withdrawal symptoms (AWS) during detoxification (n=42) indicated that whilst safe this option had no clinical benefit over placebo[5].		but no other anticonvulsant for alcohol withdrawal. **Adjunctives to benzodiazepines** New evidence, 1 trial on each of 3 adjunctives to lorazepam all indicated some benefit. However, all these agents at present are not licensed for this use and the evidence base is still limited, with regard to trial size and number. At present the evidence in this area is insufficiently robust to impact on CG100 and further research is necessary to demonstrate effectiveness of these treatments before they can be incorporated into CG100. **Muscle relaxants** The limited evidence (1 small study) available for baclofen in alcohol withdrawal is unlikely to impact on NICE CG100. Further research is necessary to demonstrate effectiveness of this treatment before it can be incorporated into CG100.

Adjunctives to benzodiazepines A RCT which compared lorazepam to ethanol/lorazepam for preventing AWS in people with myocardial infarction (n=57) indicated that both strategies had the same safety profiles and efficacy with regard to days spent in the cardiac intensive care unit and overall hospital stay[6]. A RCT which evaluated up to 5 days of dexmedetomidine (not licensed for this indication) compared to placebo as adjunctive therapy to lorazepam in a symptom triggered regimen in people (n=24) with severe alcohol withdrawal was identified[7]. The study indicated that in the short term (first 24hrs) adjunctive dexmedetomidine maintains symptom control and reduces lorazepam exposure compared to placebo but not in the long term (7 days). In addition bradycardia occurred more frequently in the dexmedetomidine group versus placebo group. A RCT indicated that a single dose of intravenous phenobarbital (not licensed for this indication) combined with a standardised lorazepam-based alcohol withdrawal protocol decreases intensive care unit admission in emergency department patients (n=102) with acute alcohol withdrawal compared to adjunctive placebo[8].		
Q: In adults and young people in acute alcohol withdrawal, what is the clinical efficacy and safety of, and patient satisfaction associated with, a) a symptom-triggered compared with a fixed-schedule benzodiazepine dose regimen b) symptom triggered compared with loading-dose regimen c) loading-dose compared with fixed-schedule regimen?		
Evidence summary	**GDG/clinical perspective**	**Impact**

Evidence Update (2012) No relevant studies identified. 4-year surveillance review (2015) A RCT which compared the efficacy of a benzodiazepine loading versus a symptom-triggered protocol in the management of alcohol withdrawal in inpatients (n=47) found that both regimens produced the same outcomes in terms of withdrawal symptom management and benzodiazepine use[9]. A second RCT which compared a fixed tapering dose with a symptom-triggered regimen of lorazepam for alcohol detoxification in male inpatients (n=63) with uncomplicated alcohol withdrawal indicated that symptom-triggered lorazepam treatment for alcohol withdrawal resulted in administration of lower total doses of medication for a shorter duration[10]. Both regimens had the same incidence of complications like seizures or delirium tremens.	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** CG100 recommends a symptom triggered regimen for drug treatment for people in acute alcohol withdrawal who are inpatients or patients in other settings with 24hr assessment and monitoring. The new evidence identified supports the effectiveness of this option and provides new evidence on the relative effectiveness of front loading. However at this time the clinical evidence for the front-loading schedule dosing is still limited as noted in the guideline with regards to sample size. Further research is necessary to demonstrate effectiveness of front-loading schedules before it can be incorporated into CG100.
Q: For the prevention and treatment of Wernicke's encephalopathy, what is: i) the safety and efficacy ii) optimum dose iii) optimum duration of treatment of a) Pabrinex b) oral b vitamin c) oral thiamine d) multivitamins e) placebo or any combinations or comparison a-e		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No relevant studies identified. 4-year surveillance review (2015) An update of a Cochrane review on thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome (WKS) in people who abuse alcohol was identified[11]. The review identified 2 studies,	Clinical feedback indicated that there had been discussions and contradictions in the public domain relating to the recommendations made in CG100 regarding the treatment of Wernicke's encephalopathy and the recommendations made subsequently in the BNF.	**No impact on recommendations.** CG100 recommends offering thiamine to people at high risk of developing, or with suspected, Wernicke's encephalopathy. Thiamine should be given in doses toward the upper end of the 'British National Formulary' range. The recommendations were made by consensus

but only 1 contained sufficient data for quantitative analysis. The study of 105 participants compared dose levels of intramuscular thiamine. Better outcomes were observed at the highest dose 200mg/day compared to lowest 5mg/day dose. However the pattern of results did not reflect a simple dose-response relationship. The review noted that this study had methodological shortcomings in design and in the presentation of results and concluded that there is insufficient evidence from RCTs to guide clinical practice around the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of WKS due to alcohol abuse.		due to the absence of RCTs on this subject. The new evidence provides supports for the recommendations on WKS. Clinical feedback indicated that there had been issues relating to the recommendation and the doses within the BNF. The doses within CG100 were decided by consensus to be at the upper limit of the BNF recommendations as the lower end (10-25mg/day) may not be adequate for individuals in a higher risk group. Following publication of CG100 the BNF reviewed the doses of thiamine and BNF 61 (March 2011) and added more specific detail on the dosing of thiamine: intravenous infusion of I/V High Potency or by deep intramuscular injection into the gluteal muscle of IM High Potency, 2 pairs [of ampoules] 3 times daily for 2 days; if no response, discontinue; if symptoms resolve after 2 days, give 1 pair [of ampoules] once daily for 5 days or for as long as improvement continues. This has been updated more recently in BNF 64 (2012), in response to comments from the manufacturer of *Pabrinex*®, and in line with the latest Maudsley guidelines (11th edition (2012)), the dose was amended to remove mention of the use of intramuscular *Pabrinex*® at the outset of treatment: *'Treatment of Wernicke's encephalopathy*, by intravenous infusion of I/V High Potency, 2–3 pairs 3 times daily for 2 days; if no response, discontinue; if symptoms respond after 2 days, give by intravenous infusion of I/V High Potency or by deep intramuscular injection.

Clinical Area 2. Alcohol related liver disease		
Q: What is the accuracy of laboratory and clinical markers versus liver biopsy for the diagnosis of alcohol-related liver disease versus other causes of liver injury?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No relevant studies identified. 4-year surveillance review (2015) A systematic and economic evaluation which assessed the diagnostic accuracy, cost-effectiveness, and effect on patient outcomes of 4 non-invasive tests for liver fibrosis (the Enhanced Liver Fibrosis (ELF) test, FibroTest , FibroMAX and transient elastography FibroScan in patients suspected of having alcohol-related liver disease (ALD)[12] was identified. The study reports that no studies were identified that specifically assessed the ELF test, 3 studies of FibroTest, no relevant studies of FibroMax, and 6 studies of FibroScan assessing accuracy compared with biopsy in patients with known or suspected alcohol-related liver disease were identified. In all studies, the number of patients with suspected ALD was small, meaning that the estimated sensitivities and specificities were not robust. A de novo mathematical model was constructed but no conclusive estimate of the cost per QALY of each non-invasive test could be provided. A systematic review and meta-analysis of diagnostic accuracy studies comparing fibroscan and aspartate transaminase to platelet ratio index (APRI) with liver biopsy for hepatic fibrosis was identified[13]. In total, 23 studies for fibroscan and	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** CG100 currently recommends that alternative causes of liver disease in people with a history of harmful or hazardous drinking who have abnormal liver blood test results should be excluded and patients referred to a specialist experienced in the management of alcohol-related liver disease to confirm a clinical diagnosis of alcohol-related liver disease. A liver biopsy can then be considered for the investigation of alcohol-related liver disease. In addition in people with suspected acute alcohol-related hepatitis, CG100 recommends considering a liver biopsy to confirm the diagnosis if the hepatitis is severe enough to require corticosteroid treatment. The new evidence from the systematic review of non-invasive tests[12] was limited and described as not robust with regards to individuals with ALD. The second study identified did not specify the numbers with ALD and as such it has a limited impact but indicates that fibroscan may be more clinically useful than APRI.

20 studies for APRI were included. For patients with stage IV fibrosis (cirrhosis), the pooled estimates for sensitivity of fibroscan were 83.4% and specificity 92.4% whereas for APRI sensitivity was 66.5% and specificity was 71.7%. However it should be noted that from the abstract it is unclear if any of the patients had alcohol dependence or harmful drinking.		
Q: What length of abstinence is needed to establish non-recovery of liver damage, which thereby necessitates referral for consideration for assessment for liver transplant?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> A RCT in people with Child–Pugh stage B alcoholic liver cirrhosis (n=120) to investigate the effect on 5-year survival of immediate listing for liver transplantation versus standard care was identified[14]. In the immediate listing group, participants (n=41) underwent transplantation at a median of 4.3 months compared to participants (n=15) in the standard-care group at a mean of 12.2 months. A case-control study in patients with medically unresponsive severe alcoholic hepatitis (n=26) looked at differences in survival between those selected for early liver transplantation and matched controls (n=26) who did not receive early transplantation[15]. In the transplantation group, 2-year survival was 71% compared with 23% in controls. <u>4-year surveillance review (2015)</u> A systematic review and meta-analysis including 7 cohort studies which examined the effect of	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** NICE CG100 recommends referral of patients for consideration of liver transplantation if they have decompensated liver disease after best management and 3 months' abstinence and are otherwise suitable candidates. The RCT identified by the Evidence Update does not suggest benefit of early transplantation, which may also be associated with detrimental outcome, lending support to this recommendation[14]. Whereas the case control study indicated a benefit, the systematic review gave no outcomes on recovery of liver damage, from an assessment of the abstract. As such the strongest relevant new evidence supports the current guideline recommendations.

abstinence from alcohol on survival of patients with alcoholic cirrhosis was identified[16]. The study indicated that it takes at least 1.5 years of alcohol abstinence before a difference in survival can be observed between the abstinent and the continue drinking groups[16].		
Q: What is the safety and efficacy of corticosteroids for acute alcohol-related hepatitis?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) A 3 month RCT which compared pentoxifylline with prednisolone in people with severe alcoholic hepatitis (n=74) found that mortality was higher with prednisolone[17]. 4-year surveillance review (2015) A RCT was identified which evaluated the addition of pentoxifylline (not licensed for this indication) to prednisolone for 28 days compared to prednisolone alone in patients who were heavy drinkers with severe biopsy-proven alcoholic hepatitis (n=270)[18]. This study found that the addition of pentoxifylline did not alter 6-month survival and at 7 days, response to therapy was not different between the 2 groups. A second study that evaluated combined pentoxifylline and prednisolone versus pentoxifylline alone in people with acute alcoholic hepatitis (n=62) found that there was no additional benefit with combination compared to monotherapy on mortality and morbidity at 1 year[19]. In addition, a systematic review (which included	Clinical feedback highlighted the STOPAH trial: a RCT of steroids or pentoxifylline or in combination in comparison to placebo in people with alcoholic hepatitis that is underway in the UK. It was noted that this trial is due to publish in early 2015.	**No impact on recommendations.** NICE CG100 recommends corticosteroid treatment for severe acute alcoholic hepatitis. The RCTs [17],[18] [19] and the systematic review on the use of pentoxifylline alone or in combination with prednisolone provide a limited and heterogeneous evidence base. As results are shortly expected from the STOPAH trial, it would be prudent to wait for this trial to publish before assessing any need to update this section of the guideline.

10 trails, n=884) indicated that pentoxifylline was more effective than placebo for the prevention of hepatorenal syndrome but provides no survival benefit at 1 month in people with severe alcoholic hepatitis[20]. However, trials of pentoxifylline versus corticosteroid, or as combination therapy did not indicate any difference in reported outcomes. A RCT which evaluated the impact of the 30 day addition of metadoxine (unlicensed for this indication), to standard treatment with glucocorticoids (prednisone) in patients with severe alcoholic hepatitis (n=70) compared to prednisone was identified[21]. Metadoxine adjunctive treatment increased 30 and 90 day survival and reduced the development or progression of encephalopathy and hepatorenal syndrome with the response to treatment being higher in those treated with metadoxine. A RCT which compared combination therapy with glucocorticoids plus N-acetylcysteine with glucocorticoids alone in patients with severe alcoholic hepatitis (n=174) found that the addition of N-acetylcysteine did not alter 6 month survival[22].		
Q: In patients with acute alcohol-related hepatitis, what is the safety and efficacy of: **a) enteral nutrition versus standard diet** **b) enteral nutrition versus corticosteroids** **c) enteral nutrition in combination with corticosteroids versus enteral diet**		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No relevant studies identified.	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** The new evidence is in line with the previous reviewed studies reported in CG100. As such the new evidence

4-year surveillance review (2015) A meta-analysis (including 7 trials) of nutritional supplementation versus diet alone for the management of hospitalised patients with alcoholic hepatitis (n=262) revealed no difference in mortality ascites or any biochemical parameter between 2 regimens[23]. However, encephalopathy showed an improvement or resolution with nutritional supplementation. A RCT comparing 8 week enteral nutrition (4 weeks) with symptomatic support in patients (n=99) with alcoholic cirrhosis and jaundice but without severe acute alcoholic hepatitis found no difference in the strategies on reported outcomes of 1 year survival and hepatic and nutritional parameters[24]. Two systematic reviews with unclear populations (not specified in abstract if participants have acute alcohol-related hepatitis) were identified: A Cochrane review (including 37 trials) on nutritional support for liver disease which assessed the beneficial and harmful effects of parenteral nutrition, enteral nutrition, and oral nutritional supplements on the mortality and morbidity of patients with underlying liver disease was identified[25]. The review reported significant effects only for the following: icteric medical patients receiving parenteral nutrition, surgical patients receiving parenteral nutrition, enteral nutrition in medical patients and oral nutritional supplements had several effects in medical patients (reduced occurrence of ascites, reduced rates of infection, and improved resolution of		supports the current recommendation to assess the nutritional requirements of people with acute alcohol-related hepatitis and offer nutritional support if needed and consider using nasogastric tube feeding.

hepatic encephalopathy. No overall effect of the supplements on mortality in medical patients was observed. The authors concluded that the data did not justify the routine use of parenteral nutrition, enteral nutrition, or oral nutritional supplements in patients with liver disease. A second systematic review and meta-analysis of RCTs (6 trials included) of oral or enteral nutritional supplementation on nutritional and clinical outcomes in adult patients with cirrhosis found that there was no reduction in mortality with this intervention[26].		
Clinical Area 3. Alcohol related Pancreatitis		
Q: **In patients with chronic alcohol-related pancreatitis, what is the safety and efficacy of a) transthoracic splanchnicectomy compared with coeliac axis/plexus block? b) or either intervention compared to conservative management?**		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) A meta-analysis (including 9 studies, n=376) which looked at pain relief after endoscopic-ultrasound directed coeliac axis block in people with chronic pancreatitis or pancreatic cancer was identified[27]. The overall proportion of patients with pain relief was 59.45%. 4-year surveillance review (2015) No relevant studies identified.	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** The evidence from the Evidence Update supports the recommendation in NICE CG100 to offer coeliac axis block to people with poorly controlled pain from non-obstructive small duct chronic alcohol-related pancreatitis, but does not add any information to guide the choice of this treatment over splanchnicectomy or surgery, which are also recommended in NICE CG100 for this population of patients.
Q: In patients with chronic alcohol-related pancreatitis, what is the safety and efficacy of endoscopic interventional procedures compared with surgery? Or either intervention compared with conservative management?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) A 5-year follow-up of a RCT in which people with symptomatic obstructive chronic pancreatitis	GDG feedback indicated that the long term data on efficacy and cost effectiveness of surgery versus endo-	**No impact on recommendations.** The results of this trial lend support to NICE CG100 which recommends offering surgery in preference to

(n=39) underwent either endoscopic or surgical drainage (pancreaticojejunostomy) of the pancreatic duct was highlighted[28]. The primary trial was stopped in 2004 because an interim analysis showed a benefit of surgical over endoscopic treatment. This report of long-term outcomes showed that the surgical group had higher pain relief compared with endoscopy. However, the pain scores seen in the surgical group were not different from the endoscopy. Of the group undergoing initial surgery, no patients developed recurrent pancreatic duct obstruction. Conversely, 9 people in the endoscopic treatment group had recurrent blockage. <u>4-year surveillance review (2015)</u> No relevant studies identified.	therapy for obstructive chronic pancreatitis was now available. This study formed part of the Evidence Update[27].	endoscopic therapy to people with pain from large-duct (obstructive) chronic alcohol-related pancreatitis.
Q: In patients with acute alcohol-related pancreatitis, what is the safety and efficacy of prophylactic antibiotics versus placebo?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> A Cochrane review of prophylactic antibiotics in patients with severe acute pancreatitis and computed tomography (CT)-confirmed necrosis included 7 studies (n=404) and found no benefit of antibiotic prophylaxis for mortality, infected pancreatic necrosis, non-pancreatic infection , overall infection, fungal infections , or need for operative treatment[29]. Similar results were seen when beta-lactams and quinolones were analysed separately. A meta-analysis of antibiotic prophylaxis in acute necrotising pancreatitis that included the studies in the above Cochrane review[29] plus a further 2	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** NICE CG100 recommends that prophylactic antibiotics should not be given to people with mild acute pancreatitis. For severe acute pancreatitis, in the CG100 the GDG considered evidence that suggested antibiotics reduced mortality. The evidence from the Evidence Update is in line with the current recommendations. **Determining severity of pancreatitis** The evidence identified in the Evidence Update was judged to be unlikely to affect NICE CG100 because the severe effects of pancreatitis were not investigated for the guideline, and the evidence from this trial does not directly influence clinical interventions for organ

RCTs had broadly similar results to those of the Cochrane review, with the exception that infected pancreatic necrosis was reduced in the antibiotic group[30] . **Determining severity of pancreatitis** A systematic review (14 studies included, n=1478) indicated that organ failure occurs in 40% and pancreatic necrosis occurs in 21% of people with acute pancreatitis with overall mortality been 13%[31]. People who had both organ failure and infected pancreatic necrosis had a higher risk of mortality than those who had only organ failure and those who only had infected pancreatic necrosis. <u>4-year surveillance review (2015)</u> No relevant studies identified.		failure or infected pancreatic necrosis.
Q: In patients with acute alcohol-related pancreatitis, what is the safety and efficacy a) of nutritional supplementation vs no nutritional supplementation b) early (first 48 hours) versus late supplementation c) NJ versus NG) versus parenteral nutrition?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> An updated Cochrane review of enteral versus parenteral nutrition (including 8 studies (2 previously) n=348) suggests that enteral nutrition reduced mortality compared with parenteral nutrition. The benefits of enteral nutrition were also seen for other outcomes including occurrence of multiple organ failure[32]. A second systematic review found that enteral nutrition when compared with, parenteral nutrition reduced the odds of having diarrhoea but increased the odds of hyperglycaemia needing	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** The evidence from the Evidence Update from the 2 systematic reviews[32,33] was included in the meta-analysis within CG100. The RCT within the Evidence Update provides results that consistently agree with NICE CG100, which recommends enteral feeding in preference to parenteral feeding if possible. More recent results indicate that the benefits of nutritional supplements may be limited to certain outcomes.

insulin administration[33]. A RCT of total enteral versus total parenteral nutrition in people with severe acute pancreatitis (n=107) on prophylactic antibiotics was identified[34]. Total parenteral nutrition increased organ failure, increased need for surgical intervention, increased pancreatic septic necrosis and mortality. . <u>4-year surveillance review (2015)</u> A meta-analysis (including 7 trials) of nutritional supplementation versus diet alone for the management of hospitalised patients with alcoholic hepatitis (n=262) revealed no difference in mortality, ascites or any biochemical parameter between 2 regimens[23]. However, encephalopathy showed an improvement or resolution with nutritional supplementation. A RCT comparing 8 week enteral nutrition with symptomatic support (4 weeks) in patients (n=99) with alcoholic cirrhosis and jaundice but without severe acute alcoholic hepatitis found no difference in the strategies on reported outcomes of 1 year survival and hepatic and nutritional parameters[24]. One systematic review with unclear populations (not specified in abstract if participants have acute alcohol-related hepatitis) was identified: the meta-analysis of RCTs (6 trials included) of oral or enteral nutritional supplementation on nutritional and clinical outcomes in adult patients with cirrhosis found that there was no reduction in		

mortality with this intervention[26].		
NEW AREA Different drugs/treatments for alcohol hepatitis		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) **Pentoxifylline for alcoholic hepatitis** A Cochrane review (including 5 trials, n=336) indicated that pentoxifylline reduced mortality compared with control and reduced mortality due to hepatorenal syndrome in the meta-analysis[35]. 4-year surveillance review (2015) A systematic review (which included 10 trials, n=884) indicated that pentoxifylline was more effective than placebo for the prevention of hepatorenal syndrome but provides no survival benefit at 1 month in patients with severe alcoholic hepatitis[20]. A RCT in patients with severe alcoholic hepatitis (n=50) compared 28 days of pentoxifylline (not licensed for this indication) or placebo found no difference in terms of short term mortality[36]. A sub-analysis of the Study of Ascending Levels of tolvaptan (not licensed for this indication) trials which compared 30 day oral tolvaptan to placebo in cirrhotic patients (n =120) indicates that this is an effective treatment to raise serum sodium[37]. However hyponatremia recurred 7 days after discontinuation of tolvaptan. A RCT in patients (n=85) with compensated alcoholic liver fibrosis indicated that patients that received candesartan (not licensed for this	No GDG feedback was provided by the GDG questionnaire.	**No impact on recommendations.** NICE CG100 recommends corticosteroid treatment for severe acute alcoholic hepatitis. The evidence with regards to the effectiveness of pentoxifylline is heterogeneous. As this agent is currently not licensed for this indication further research is necessary to demonstrate effectiveness before it can be incorporated into CG100. In addition, results are shortly expected from the STOPAH trial, therefore consideration of additional drugs should wait until this large UK trial published. The evidence for the use of tolvaptan and autologous bone marrow mononuclear cell transplantation indicates that these are not effective options. The use of candesartan with ursodeoxycholic acid is still limited and further research is necessary to demonstrate effectiveness before it can be incorporated into CG100.

indication) with ursodeoxycholic acid for 6 months had higher rates of histological improvements than those who received ursodeoxycholic acid alone[38]. A RCT in patients (n=58) with decompensated alcoholic liver disease found that autologous bone marrow mononuclear cell transplantation did not improve liver function or regeneration compared to standard medical therapy (including steroids)[39].		

For the following areas of CG100 no new evidence was identified:

- What are the benefits and risks of unplanned 'emergency' withdrawal from alcohol in acute medical settings versus discharge?
- What criteria (e.g. previous treatment, homelessness, levels of home support, age group) should be used to admit a patient with acute alcohol withdrawal for unplanned emergency withdrawal from alcohol?
- What assessment tools, including clinical judgement, are associated with improved clinical and patient outcomes when using a symptom-triggered dose regimen in patients with acute alcohol withdrawal?
- What is the safety and efficacy of a) neuroleptic agents, promazine hydrochloride, haloperidol, clozapine, risperidone, olanzapine, quetiapine) versus placebo b) other neuroleptic agents c) neurolepetic agents in combination with benzodiazepines (diazepam, chlordiazepoxide, alprazolam, oxazepam, clobazam, lorazepam) for patients with DTs?"
- What is the safety and efficacy of benzodiazepines versus a) placebo b) other benzodiazepines c) other anticonvulsants for the prevention of recurrent seizures during acute alcohol withdrawal?
- What is the accuracy of a tool and/or clinical judgement for the a) assessment b) monitoring of patients who are alcohol dependent and therefore at risk of developing acute alcohol withdrawal?
- Does the assessment and monitoring of patients with acute alcohol withdrawal improve patient outcomes?
- Which patients are at risk of developing Wernicke's encephalopathy and therefore require prophylactic treatment?
- What is the safety and accuracy of laboratory and clinical markers versus liver biopsy for the diagnosis of alcohol related hepatitis versus decompensated cirrhosis?
- In patients with acute alcohol-related hepatitis, what is the safety and efficacy of corticosteroids versus placebo?
- What is the diagnostic accuracy of abdominal ultrasound versus computed tomography (CT) for the diagnosis of alcohol-related chronic pancreatitis?

- In patients with chronic alcohol-related pancreatitis, does early versus later referral for a) coeliac axis block b) transthoracic splanchnicectomy c) early referral for coeliac axis/plexus block versus transthoracic splanchnicectomy improve patient outcomes?
- In patients with chronic alcohol-related pancreatitis, does early versus later referral for a) endoscopic interventional procedures b) surgery c) early referral for surgery versus endoscopic interventional procedures improve patient outcomes?
- In patients with chronic alcohol-related pancreatitis, what is the safety and efficacy of pancreatic enzyme supplementation versus placebo for a) steatorrhoea and weight gain b) abdominal pain, duration of pain episodes, intensity of pain and analgesic use for pancreatic exocrine insufficiency?

NICE guideline on alcohol dependence and harmful alcohol use (CG115)

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the NICE guideline on alcohol dependence and harmful alcohol use. This guideline covers assessment, pharmacological interventions, psychological and psychosocial interventions, and settings of assisted withdrawal and rehabilitation.

Clinical Area 1. Experience of care		
Q. For families and carers of people who misuse alcohol, what are their experiences of caring for people with an alcohol problem and what support is available for families and carers?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2013) A systematic review (21 studies, n=1500) found 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[40]. 4-year surveillance review (2015) No relevant studies identified.	No GDG feedback was provided through the GDG questionnaire.	**No impact on recommendations.** NICE CG115 recommends offering families and carers who are involved in supporting a person who misuses alcohol 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. The findings of the systematic review identified by the Evidence Update are consistent with these recommendations.
Clinical Area 2. Evaluating the organisation of care for people who misuse alcohol		
Q. In adults with alcohol misuse, what is the clinical efficacy, cost effectiveness, and safety of, and patient satisfaction associated with different systems for the organisation of care?		

Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2013) No relevant studies identified. 4-year surveillance review (2015) One RCT was identified which evaluated the effectiveness of Chronic care management (CCM) (including longitudinal care coordinated with a primary care clinician; motivational enhancement therapy; counselling, addiction and psychiatric treatment, and social work assistance) for improving care and outcomes in people with alcohol and other drug dependence (n=563). The results showed no difference in self-reported abstinence between CCM and no CCM (a primary care appointment and a list of treatment resources)[41]. Another RCT (n=163) was identified which tested the effectiveness of a primary care-based Alcohol Care Management (ACM) programme, delivered in-person or by telephone, for alcohol-dependent veterans. The results showed that ACM increased rates of engagement in treatment and reduced heavy drinking compared to standard treatment in an outpatient addiction treatment programme[42].	No GDG feedback was provided through the GDG questionnaire.	**No impact on recommendations.** The new evidence is consistent with NICE CG115 which recommends for all people who misuse alcohol, offer interventions to promote abstinence or moderate drinking as appropriate and prevent relapse, in community-based settings. This includes psychological interventions for harmful drinkers and people with mild alcohol dependence.
Clinical Area 3. The assessment of harmful drinking and alcohol dependence		
Q. To answer questions 4 and 5, what are the advantages, disadvantages, and clinical utility of: • **the structure of the overall clinical assessment** • **biological measures** • **psychological/behavioural measures** • **neuropsychiatric measures (including cognitive impairment)** • **physical assessment?**		

Evidence summary	GDG/clinical perspective	Impact
Evidence Update (2013) No relevant studies identified. 4-year surveillance review (2015) A systematic review and meta-analysis (15 studies) was identified which evaluated the use of ethyl glucuronide (HEtG) as a marker in hair for identifying chronic excessive drinking and for monitoring abstinence. The review found differing levels of HEtG concentrations in hair between drinking groups, with increased levels in heavy and chronic excessive drinkers compared to social drinkers[43].	No GDG feedback was provided through the GDG questionnaire.	**No impact on recommendations.** The guideline found no evidence to support the use of hair analysis for diagnosis, assessment and monitoring clinical progress in alcohol dependence and harmful alcohol use. Whilst the new evidence indicates that HEtG is a promising marker for identifying excessive drinking and monitoring abstinence, further consistent evidence is needed to demonstrate effectiveness before it can considered for inclusion in CG115.
Clinical Area 4. Determining the appropriate setting for the delivery of effective care		
Q. In adults in planned alcohol withdrawal, what is the clinical efficacy, cost effectiveness, safety of, and patient satisfaction associated with: • **preparatory work before withdrawal** • **different drug regimens** • **the setting (that is, community, residential or inpatient)?**		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2013) A RCT assessing the use of chlordiazepoxide in alcohol-dependent patients (n=165) undergoing outpatient alcohol withdrawal was identified. The study found no difference in treatment effectiveness between a fixed-dose and symptom-triggered drug regimen[44]. A Cochrane review (including 13 RCTs, n=648) examining gamma-hydroxybutyrate (GHB) for alcohol withdrawal found insufficient evidence of a difference in efficacy	No GDG feedback was provided through the GDG questionnaire.	**No impact on recommendations.** NICE CG115 recommends that fixed-dose medication regimens should be used in community-based assisted withdrawal programmes. The evidence from the Evidence Update found no difference in treatment effectiveness between the two regimens in an outpatient setting therefore it is unlikely to impact on the current recommendation. In relation to the use of GHB for alcohol

between GHB and placebo and other drugs. It also highlighted concerns about dependence and risk of misuse or abuse of GHB[45]. 4-year surveillance review (2015) No relevant studies identified.		withdrawal, the evidence from the Evidence Update is consistent with the recommendations in NICE CG115, which states 'do not use GHB for the treatment of alcohol misuse'.
Clinical Area 5. Psychological and psychosocial interventions		
Q. For people with alcohol dependence or who are harmful drinkers, is psychological *treatment x* when compared with *y*, more clinically and cost effective and does this depend on: • **presence of comorbidities** • **subtypes (matching effects)** • **therapist-related factors (quality, therapeutic alliance, competence, training, and so on).**		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2013) **Couples therapy** A systematic review (13 studies, n=1200) found that couples therapy resulted in positive outcomes, especially in drinking behaviour and marital adjustment, and that using a therapeutic approach can positively influence the success of the intervention[40]. **Motivational techniques** A RCT (n=138) was identified which compared treatment as usual, a motivation enhancement therapy (MET) and a peer-delivered twelve-step facilitation (P-TSF) intervention during alcohol detoxification. The results of the study showed MET was more effective than treatment as usual and P-TSF in term of initiating and maintaining patients in aftercare inpatient treatment programmes which is consistent with the recommendations	Clinical feedback indicated that there are issues relating to the implementation of the recommendations relating to psychological treatments, stating that they represent the gold standard but are not always achievable in the current climate. It was highlighted that the guidance on the delivery of psychological treatment interventions as a necessary requirement for any prescribing of pharmacological therapies should therefore be reviewed.	**No impact on recommendations.** **12-step facilitation** The evidence at the 4 year surveillance review is in line with the previous reviewed studies reported in CG115 which found no evidence to support a recommendation for 12-Step facilitation. As such, the new evidence is unlikely to impact on current recommendations relating to psychological treatments for alcohol misuse. **Behavioural therapies** NICE CG115 recommends for harmful drinkers and people with mild alcohol dependence, offer 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

in the guideline relating to motivational interviewing[46]. **Telephone monitoring** A substudy of an RCT (n=252) evaluating potential moderators of the effect of adding telephone monitoring or telephone monitoring and counselling to treatment as usual for the treatment of alcohol dependence was identified. Moderator variables included years of regular alcohol use, years of heavy alcohol use, number of prior treatments for alcohol problems, days of alcohol use and heavy alcohol use. The study found that none of the variables interacted with treatment type to predict frequency of alcohol use and that there was no prediction of alcohol use versus abstinence. However, there were significant moderation effects favouring telephone monitoring over treatment as usual in terms of readiness for change[47]. **Psychological therapies and co-morbidities** A systematic review (including 8 RCTs, n=831) evaluating psychological interventions for alcohol misuse among people with co-occurring depressive or anxiety disorders was identified. The review indicated that psychological interventions, including motivational interviewing and CBT, were effective in reducing alcohol consumption and depressive and/or anxiety symptoms[48]. A RCT investigating an intervention to reduce		networks. The evidence identified at the 4 year surveillance review is in line with the evidence in NICE CG115 and supports the current recommendation. **Contingency management** The limited evidence (1 small study) identified at the 4 year surveillance review is in line with the evidence in CG115 which found that the addition of contingency management to standard care was beneficial in reducing the number of participants who relapsed to heavy drinking. However, the evidence is insufficient to answer the research recommendation which stated that the study should report short-and medium-term outcomes of at least 18 months' duration; and needs to be large enough to determine the presence or absence of clinically important effects. Further consistent evidence is needed to demonstrate effectiveness before it can considered for inclusion in CG115. **Couples therapy** The evidence from the Evidence Update supports the current recommendation relating to behavioural couples therapy for harmful drinkers and people with mild alcohol dependence who have a regular partner who is willing to participate in treatment. **Motivational techniques** The evidence from the RCT in the Evidence Update and the 3 RCTs identified at the 4 year surveillance review support NICE CG115

alcohol consumption in people admitted to hospital for alcohol-related acute pancreatitis (n = 120) was identified. The intervention consisted of a 30-minute conversation covering the toxic effects of alcohol on the pancreas, the need to change drinking habits, and social problems faced by participants. Overall, 15% of participants were readmitted in 2 years including 8.5% in the intervention group and 21.3% in the control group[49]. <u>4-year surveillance review (2015)</u> **12-step facilitation** One RCT indicated that active referral to 12-Step self-help interventions delivered by doctors or peers were no more effective than no intervention in increasing abstinence rates in inpatients with alcohol and other substance dependence (n=151)[50]. **Behavioural therapies** A systematic review and meta-analysis (including 23 trials) which evaluated the benefits of behavioural counselling interventions for alcohol misuse indicated that there was a reduction in alcohol consumption in adults receiving behavioural interventions compared with controls[51]. **Contingency management** One RCT of a portable Contingency management (CM) procedure using a mobile phone and breathalyser in non-dependent, frequent drinking adults (n=30) was identified.		which recommends providing an intervention containing the key elements of motivational interviewing. **Telephone monitoring** The results of the study in the Evidence Update suggest that although telephone monitoring and counselling produced the best alcohol use outcomes there were no moderators that interacted significantly with treatment type. The evidence 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 telephone monitoring and counselling 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. **Self-help based treatment** The RCTs identified at the 4 year surveillance review relating to mobile phone and web-based applications for the treatment of alcohol disorders provides a limited and heterogeneous evidence base. Further consistent evidence is needed before these new technologies can be considered for inclusion within the guideline. **Psychological therapies and co-morbidities** Psychological interventions for co-morbid alcohol dependence and mental health

The study found no differences between groups receiving modest compensation or compensation plus CM and vouchers for the submission of on-time alcohol concentration breath tests. However, rates of negative breath tests and duration of abstinence were higher in the CM group[52]. **Psychological therapies and co-morbidities** A RCT (n=62) found that integrated CBT for co-morbid post-traumatic stress disorder (PTSD) and alcohol use disorders (AUD) was more effective at reducing PTSD severity compared with CBT for AUD plus supportive counselling[53]. Another study, a systematic review (12 studies, n=1721) examined a combined CBT/motivational interviewing (MI) intervention to treat comorbid AUD and major depression. The results indicated that compared with usual care, CBT/MI reduced alcohol consumption and symptoms of depression[54]. **Motivational techniques** Three RCTs were identified which indicated that different types of motivational techniques (motivational enhancement therapy (MET), a brief motivational intervention (BMI) plus telephone booster and telephone-based BMI) were effective in reducing alcohol consumption and increasing abstinence in people with alcohol problems[55-57]. **Self-help based treatment**		problems, such as depression or anxiety, are out of scope of NICE CG115. However, the evidence from the Evidence Update and the 4 year surveillance review is consistent with NICE CG115 which recommends psychological programmes (motivational interviewing and cognitive behavioural interventions) for people with alcohol misuse or dependence. The RCT identified in the Evidence Update investigating an intervention to reduce alcohol consumption in people admitted to hospital for alcohol-related acute pancreatitis is unlikely to impact on NICE CG115 which recommends interventions to promote abstinence or moderate drinking as appropriate and prevent relapse. **Brain stimulation** The limited evidence (1 small study) identified at the 4 year surveillance review for repetitive transcranial direct current stimulation is unlikely to impact on current guideline recommendations for the treatment of alcohol misuse. Further consistent evidence is needed to demonstrate effectiveness before it can considered for inclusion in CG115.

A RCT investigating the use of a smartphone application to support recovery (both during residential care and continuing care after discharge) compared to treatment as usual (none offered patients coordinated continuing care) in patients with alcohol dependence (n=349) was identified. The smartphone application reduced risky drinking days at both 4 and 8 months[58]. Whereas a RCT of an 8 week short message service mobile phone based intervention in detoxified alcohol-dependent patients (n=80) for relapse prevention found that whilst the text messaging was feasible and acceptable it did not reduce alcohol consumption more than treatment as usual[59]. A RCT in patients who completed an in-patient dual diagnosis treatment programme for depression and co-morbid alcohol use disorder (n=54) indicated that twice daily supportive text messages improved both depression related outcomes and alcohol abstinence compared to control[60]. A second report from this study indicated that patients perceived the intervention as motivational for recovery and in preventing relapse[61]. However, a further report on 6 month outcomes found that the beneficial effects of the supportive text message intervention were not sustained beyond the period that the patients were receiving the intervention[62]. A further RCT in participants classed as heavy problem drinkers (n=189) investigated		

the use a cognitive behavioural Web-based application alone or in combination with in-person mutual help groups in comparison to mutual help groups heavy problem drinkers. At 3 months all groups increased their percentage of days abstinent, decreased their mean drinks per drinking day and decreased their alcohol/drug-related problems[63]. **Brain stimulation** The results of a RCT indicated that repetitive transcranial direct current stimulation (tDCS) was more effective than control (sham-tDCS) in reducing the risk of relapse and improving quality of life in severe alcoholics in outpatient services (n=33)[64].		
Clinical Area 6. Pharmacological interventions		
Q. For people with alcohol dependence or harmful alcohol use, what pharmacological interventions are more clinically and cost effective? In addition: **(a) What are the impacts of severity and comorbities on outcomes?** **(b) When should pharmacological treatments be initiated and for what duration should they be prescribed?**		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2013) A study evaluating the broader social outcomes and costs of combinations of pharmacotherapies and behavioural therapies (from the Combined Pharmacotherapies and Behavioural Intervention (COMBINE) RCT) over 3 years was identified. The study found at 3 years, the median costs of medical management plus combined therapies were significantly lower than the median cost for medical management plus placebo[65].	The GDG identified the following ongoing trials relating to Baclofen: • Efficacy and Safety of Baclofen for Maintenance of Abstinence in Alcohol Dependent Patients (ALPADIR) • Baclofen for the Treatment of Alcohol Drinkers (BACLOVILLE) GDG feedback highlighted that a change in the guideline may be required to take account of TA325: nalmefene for reducing alcohol consumption in people with alcohol	**No impact on recommendations.** **Pharmacological interventions licensed for alcohol use - Acamprosate and Disulfiram** NICE CG115 recommends acamprosate or oral naltrexone in combination with an individual psychological intervention for people with moderate and severe alcohol dependence after a successful withdrawal from alcohol. Evidence identified at the 4 year surveillance review indicates that acamprosate has no clinical benefit over

Antipsychotics A RCT comparing quetiapine with placebo in alcohol dependent patients (n=218) found no differences in drinking outcomes, alcohol craving and anxiety between the two groups. However, quetiapine did lead to greater improvements in depression and sleep quality compared to placebo[66]. **Baclofen** A RCT which compared baclofen (not licensed for this indication) with placebo for the treatment of alcohol dependence found no differences between groups (n=80) in terms of average rates of heavy drinking, the proportion of abstinent days, craving, depression or anxiety[67]. **Anticonvulsants** A RCT evaluating the tolerability and effectiveness of topiramate compared with naltrexone in people (n=91) with alcohol dependence was identified. At 6 months, there were no significant differences between topiramate and naltrexone in terms of abstinence, percentage days abstinent, or total drinking days. However, in the topiramate group there was significantly more moderate drinking without problems, significantly fewer drinks per drinking day and significantly fewer heavy drinking days[68]. **SSRIs** Two RCTs (n=134) were identified which	dependence within the recommended care pathway for the treatment of alcohol dependence within CG115. Currently nalmefene is not included in the pathway described in the guideline as a treatment option. As a result there is potential confusion about where nalmefene fits relative to other pharmacotherapies.	placebo in terms of abstinence or heavy drinking. However, the evidence for acamprosate in the guideline was based on large, high quality studies, therefore it is unlikely that this new evidence will impact on the current recommendations in the guideline. The evidence from the systematic review identified through this surveillance is in line with CG115 which found little evidence to suggest a benefit of one drug over the other. The limited evidence (1 small study) identified for disulfiram is unlikely to impact on NICE CG115 which recommends disulfiram as a second-line treatment option for moderate to severe alcohol dependence for people for whom acamprosate or naltrexone are not suitable, or who have specified a preference for disulfiram. **Baclofen** During development of NICE CG115, limited evidence of the efficacy of baclofen as a pharmacological intervention for alcohol dependence was identified. The new evidence identified through the Evidence Update and 4 year surveillance review is heterogeneous. Furthermore, baclofen is currently not licensed for this indication. The results from ongoing studies are expected to be published in early 2015, therefore it would be prudent to wait for these studies to publish before assessing any need to update this section of the guideline.

evaluated the effectiveness of sertraline for the treatment of alcohol dependence (defined as either late-onset or early-onset) alongside the moderating effects of a functional polymorphism in the serotonin transporter gene. The trials found at the end of treatment and at 3 month follow up that sertraline reduced alcohol consumption in the late-onset group in those with the homozygous LL allele. In the early-onset group, greater reductions in drinking were observed with placebo, however this effect was no longer significant at 3 months. No significant treatment effects were seen in those with the S allele[69,70]. **Genetic polymorphisms – ondansetron** A RCT which evaluated ondansetron plus standardised CBT was identified. Participants (n=283) were designated as having a LL, LS or SS genotype. The results indicated that individuals with the LL genotype who received ondansetron had reduced alcohol consumption and increased abstinence compared with those who received placebo and to other genotypes[71]. **Pharmacological interventions and co-morbidities** A meta-analysis (including 11 RCTs), n=891) found that antidepressants were more effective than placebo in the treatment of depression in patients with comorbid alcohol use disorders[72]. <u>4-year surveillance review (2015)</u>		**Antipsychotics** The new evidence identified through the Evidence Update and 4 year surveillance review indicates that antipsychotics are not effective for improving alcohol related outcomes in people with alcohol dependence. The evidence is therefore unlikely to impact on current guideline recommendations. **Anticonvulsants** The new evidence identified by the Evidence Update and 4 year surveillance review relating to the effectiveness of anticonvulsants for alcohol dependency is heterogeneous. In addition, none of the drugs are currently licensed for this indication. It is therefore unlikely that the new evidence will impact on current guideline recommendations. **Benfotiamine** The limited evidence (1 small study) available for benfotiamine is unlikely to impact on NICE CG115. Further consistent evidence is needed before it can be considered for inclusion in the guideline. **LY2196044** The evidence identified relating to LY2196044 found no clinical benefit of the drug over placebo, therefore it is unlikely to impact on current recommendations. **Varenicline** New evidence indicates that varenicline is more effective than placebo and a

Related NICE guidance: • Nalmefene for reducing alcohol consumption in people with alcohol dependence (TA325) **Acamprosate** One RCT comparing oral acamprosate and placebo in the treatment of alcohol-dependent patients (n=100) in a family medicine setting was identified. The study revealed no differences in abstinence or heavy drinking between the two groups[73]. The results of a systematic review and meta-analysis also showed that there were no differences between acamprosate and naltrexone for controlling alcohol consumption in adults with alcohol use disorders[74]. **Disulfiram** A RCT found that disulfiram was superior to naltrexone for promoting abstinence in adolescents with alcohol dependence (n=52)[75]. **Anticonvulsants** A systematic review assessing the benefits of anticonvulsants for the treatment of alcohol dependence (25 studies, n=2641) was identified. Findings indicated that anticonvulsants had no clinical benefit over placebo and naltrexone in terms of rates of continuous abstinence. However, there was some evidence showing that anticonvulsants reduced alcohol consumption compared to		computerised behavioural intervention for the treatment of alcohol dependence. Varenicline is not currently licensed for this indication, therefore the evidence is unlikely to impact on current recommendations. **Nalmefene** The NICE guidance on nalmefene for reducing alcohol consumption in people with alcohol dependence (TA325) currently recommends nalmefene as an option for reducing alcohol consumption, for people with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification. The new evidence identified for nalmefene, including 3 studies which formed the evidence base for TA325, is unlikely to impact on the current guideline recommendations in CG115 which covers pharmacological interventions for people with moderate and severe alcohol dependence after a successful withdrawal from alcohol. Clinical feedback indicated that an update of the guideline may be needed to take account of TA325 within the recommended care pathway for the treatment of alcohol dependence within CG115. However, TA325 is included as a treatment option within the NICE pathway on interventions for harmful drinking and mild alcohol dependence. **Combined Pharmacotherapies** The study from the Evidence Update is from

placebo and naltrexone[76]. Two systematic reviews and meta-analyses and a RCT were identified which found that topiramate is more effective than placebo in reducing alcohol consumption and increasing abstinence in people with alcohol use disorders[74,77,78]. Whereas the results of a RCT examining the efficacy of topiramate for patients receiving a residential treatment programme of alcohol detoxification and post-acute treatment (n=53) indicated that there were no differences in outcomes between topiramate and placebo in terms of percentages of heavy drinking days and time to first day of heavy drinking[79]. A RCT comparing the anticonvulsant levetiracetam with placebo in heavy drinking alcohol-dependent patients (n=130) found no differences in outcomes in terms of alcohol consumption[80]. One RCT found that oral gabapentin increased rates of abstinence and reduced alcohol consumption in adults with alcohol dependence (n=150). Improved outcomes were associated with increased dose[81]. **Antipsychotics** One RCT indicated that adding a brief-alcohol-intervention (BI) to paroxetine was not effective in reducing alcohol use in at-risk drinkers with a social anxiety disorder (n=83)[82].		the USA and so the utilised costs may not be directly relevant to the UK. However, the study demonstrates the reduction in social costs achieved through the use of alcohol treatment in alcohol dependent people and is consistent with NICE CG115. **Genetic polymorphisms – ondansetron** 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. **SSRIs** NICE CG115 recommends that antidepressants (including selective serotonin reuptake inhibitors [SSRIs]) should not be used routinely for the treatment of alcohol misuse alone. They are also currently not licensed for this indication. Whilst the Evidence Update found some evidence of effectiveness for sertraline in individuals with the homozygous LL allele, the authors of the study 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 the current guideline recommendations.

One RCT indicated that quetiapine was not effective at reducing alcohol consumption in outpatients with bipolar I or II disorders, depressed or mixed mood state, and current alcohol dependence (n=90)[83]. A systematic review and meta-analysis including patients with alcohol dependence (13 trials, n=1593) revealed that antipsychotics have no clinical benefit over placebo in terms of relapse prevention, alcohol consumption and craving[84]. **Baclofen** The results of a post-hoc analysis of a RCT showed that baclofen (not licensed for this indication) increased the rate of total alcohol abstinence compared with placebo in a subgroup of alcohol-dependent Hepatitis C virus-infected cirrhotic patients (n=24)[85]. Another RCT (n=42) examining the effectiveness of baclofen for the treatment of alcohol dependence was identified. The results indicated that baclofen has no benefit over placebo in terms of relapse prevention. However, post hoc analysis showed a beneficial effect of baclofen over placebo on time to lapse and relapse in alcohol-dependent individuals with comorbid anxiety disorder[86]. **Benfotiamine** One RCT was identified which examined the effect of benfotiamine (high-potency thiamine;		**Pharmacological interventions and co-morbidities** The Evidence Update concluded that due to the limitations of the study relating to antidepressant use for the treatment of depression in patients with co-morbid alcohol use disorders, the evidence is unlikely to have an impact on NICE CG115. Furthermore, NICE CG115 recommends that for the treatment of comorbid mental health disorders refer to the relevant NICE guideline for the particular disorder.

not licensed for this indication) on alcohol consumption in severely alcohol dependent adults (n=70). Over 6 months the trial demonstrated that benfotiamine was more effective than placebo in reducing alcohol consumption in women. However, no outcomes were reported in the abstract relating to male participants[87]. **LY2196044** A RCT comparing LY2196044 (an opioid receptor antagonist; not licensed for this indication) in combination with medical management with placebo in alcohol-dependent adults (n=375) found no differences in drinking outcomes between the two groups[88]. **Varenicline** One RCT (n = 200) comparing the efficacy of varenicline (not licensed for this indication) for the treatment of alcohol dependence found that it reduced alcohol consumption and craving compared to placebo and a computerised behavioural intervention[89]. **Nalmefene** A systematic review and meta-analysis found that nalmefene improves alcohol consumption outcomes, in terms of the number of heavy drinking days per month and drinks per drinking day, in adults with alcohol use disorders[74]. A number of reports from the ESENSE 1,		

ESENSE 2 and SENSE trials which formed the evidence base for TA325 were identified: • A report from the SENSE trial: a RCT in patients with alcohol dependence (n=675) which compared 52 weeks of as-needed treatment with placebo or nalmefene indicated that at 13 months of nalmefene treatment was more effective than placebo, both in the reduction of the number of heavy drinking days and the reduction of total alcohol consumption. However, this effect was not apparent at 6 months[90]. • A report from the ESENSE 1 24 week as-needed nalmefene versus placebo RCT in patients with alcohol dependence (n=718) and medium drinking risk indicated that nalmefene was effective in reducing heavy drinking days at 6 months but not in reducing total alcohol consumption[91]. A report from the ESENSE2 trial, a RCT of 24 weeks of as-needed placebo or nalmefene in patients with alcohol dependence (n=604) and average alcohol consumption indicates that nalmefene was effective in reducing the number of heavy drinking days and total alcohol consumption at 6 months[92]. • A subgroup analysis in the population taken from both the ESENSE 1 and ESENSE 2 trials of patients (n=667) with at least a high drinking risk level (men: >60 g/day; women: >40 g/day) indicates that nalmefene is effective in reducing the number of heavy drinking days and total		

alcohol consumption at 6 months. Improvements in clinical status and liver parameters were greater in the nalmefene group compared with the placebo group[93]. • A cost-effectiveness analysis of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels was developed based on data from RCTs: ESENSE 1, ESENSE 2 and SENSE. The Markov model indicated nalmefene in combination with psychosocial support had an ICER of £5204 per QALY gained, and was therefore cost-effective[94].		

For the following areas of the CG115 no new evidence was identified:

- For people who misuse alcohol, what are their experiences of having problems with alcohol, of access to services and of treatment?
- What are the most effective (a) diagnostic and (b) assessment tools for alcohol dependence and harmful alcohol use?
- What are the most effective ways of monitoring clinical progress in alcohol dependence and harmful alcohol use?
- What are the most effective (a) diagnostic and (b) assessment tools for alcohol dependence and harmful alcohol use in children and young people (aged 10–18 years)?
- What are the most effective ways of monitoring clinical progress in alcohol dependence and harmful alcohol use in children and young people (aged 10–18 years)?
- In adults in planned alcohol withdrawal what factors influence the choice of setting in terms of clinical and cost effectiveness including:
    - severity of the alcohol disorder
    - physical comorbidities
    - psychological comorbidities
    - social factors
- In adults with harmful or dependent alcohol use what are the preferred structures for and components of community-based and residential specialist alcohol services to promote long-term clinical and cost-effective outcomes?
- For children and young people with alcohol dependence or harmful alcohol use is treatment x when compared with y more clinically and cost effective and does this depend on the presence of comorbidities?

Ongoing research

- HTA - 13/86/03: The effectiveness of adjunctive Medication Management and Contingency Management to enhance adherence to medications for relapse prevention in alcohol dependence. Estimated publication date June 2019. Developed in response to one of the research recommendations from CG115.
- HTA - 11/60/01: Adaptation and feasibility study of a family and social network intervention for young people who misuse alcohol and drugs. Estimated publication date June 2016. This is a pilot study which aims to tackle the gap in the evidence base for effective interventions for young people (relevant to CG115).
- Efficacy and Safety of Baclofen for Maintenance of Abstinence in Alcohol Dependent Patients (ALPADIR). Trial completed end 2014, awaiting publication (relevant to CG115).
- Baclofen for the Treatment of Alcohol Drinkers (BACLOVILLE) (relevant to CG115).
- STOPAH trial: a multicentre, double-blind RCT comparing placebo to prednisolone or pentoxifylline and prednisolone combined has recently completed and is due to publish as a series of papers in the first half of 2015 (relevant to CG100).

Anti-discrimination and equalities considerations

None identified.

Conclusion

Through the 4 year surveillance review of CG100 and CG115 no new evidence which may potentially change the direction of guideline recommendations was identified. The proposal is not to update these guidelines at this time.

References

1. Amato L, Minozzi S, Vecchi S et al. (2010) Benzodiazepines for alcohol withdrawal. Cochrane Database of Systematic Reviews CD005063.

2. Minozzi S, Amato L, Vecchi S et al. (2010) Anticonvulsants for alcohol withdrawal. Cochrane Database of Systematic Reviews CD005064.

3. Liu J and Wang L. (2011) Baclofen for alcohol withdrawal. Cochrane Database of Systematic Reviews 1:CD008502.

4. Rajmohan V, Sushil K, and Mohandas E. (2013) A double blind randomised comparison of chlordiazepoxide and lorazepam in alcohol withdrawal. Asian Journal of Psychiatry 6:401-403.

5. Forg A, Hein J, Volkmar K et al. (2012) Efficacy and safety of pregabalin in the treatment of alcohol withdrawal syndrome: a randomized placebo-controlled trial. Alcohol & Alcoholism 47:149-155.

6. Fullwood JE, Mostaghimi Z, Granger CB et al. (2013) Alcohol withdrawal prevention: a randomized evaluation of lorazepam and ethanol--a pilot study. American Journal of Critical Care 22:398-406.

7. Mueller SW, Preslaski CR, Kiser TH et al. (2014) A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Critical Care Medicine 42:1131-1139.

8. Rosenson J, Clements C, Simon B et al. (2013) Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. Journal of Emergency Medicine 44:592-598.

9. Maldonado JR, Nguyen LH, Schader EM et al. (2012) Benzodiazepine loading versus symptom-triggered treatment of alcohol withdrawal: a prospective, randomized clinical trial. General Hospital Psychiatry 34:611-617.

10. Sachdeva A, Chandra M, and Deshpande SN. (2014) A comparative study of fixed tapering dose regimen versus symptom-triggered regimen of lorazepam for alcohol detoxification. Alcohol & Alcoholism 49:287-291.

11. Day E, Bentham PW, Callaghan R et al. (2013) Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. SO: Cochrane Database of Systematic Reviews .

12. Stevenson M, Lloyd-Jones M, Morgan MY et al. (2012) Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. [Review]. Health Technology Assessment (Winchester, England) 16:1-174.

13. Abd El Rihim AY, Omar RF, Fathalah W et al. (2013) Role of fibroscan and APRI in detection of liver fibrosis: A systematic review and meta-analysis. Arab Journal of Gastroenterology 14:44-50.

14. Vanlemmens C, Di M, V, Milan C et al. (3-2-2009) Immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis: a randomized trial. Annals of Internal Medicine 150:153-161.

15. Mathurin P MCDD. (1-9-2011) Early liver transplantation for severe alcoholic hepatitis. New England Journal of Medicine 365:1790-1800.

16. Xie Y-D, Feng B, Gao Y et al. (2014) Effect of abstinence from alcohol on survival of patients with alcoholic cirrhosis: A systematic review and meta-analysis. Hepatology Research 44:436-449.

17. De BK, Gangopadhyay S, Dutta D et al. (7-4-2009) Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World Journal of Gastroenterology 15:1613-1619.

18. Mathurin P, Louvet A, Duhamel A et al. (11-9-2013) Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA 310:1033-1041.

19. De B, Mandal S, Sau D et al. (2014) Pentoxifylline Plus Prednisolone versus Pentoxifylline Only for Severe Alcoholic Hepatitis: A Randomized Controlled Clinical Trial. Annals of Medical & Health Sciences Research 4:810-816.

20. Parker R, Armstrong MJ, Corbett C et al. (2013) Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. [Review]. Alimentary Pharmacology & Therapeutics 37:845-854.

21. Higuera DD-T, Servin-Caamano AI, Cruz HJ et al. (2014) Treatment with metadoxine and its impact on early mortality in patients with severe alcoholic Hepatitis. SO: Annals of hepatology 13:343-352.

22. Nguyen KE, Thevenot T, Piquet MA et al. (2011) Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. SO: New England journal of medicine 365:1781-1789.

23. Antar R, Wong P, and Ghali P. (2012) A meta-analysis of nutritional supplementation for management of hospitalized alcoholic hepatitis. Canadian Journal of Gastroenterology 26:463-467.

24. Dupont B, Dao T, Joubert C et al. (2012) Randomised clinical trial: enteral nutrition does not improve the long-term outcome of alcoholic cirrhotic patients with jaundice. Alimentary Pharmacology & Therapeutics 35:1166-1174.

25. Koretz RL, Avenell A, and Lipman TO. (2012) Nutritional support for liver disease. [Review]. Cochrane Database of Systematic Reviews 5:CD008344.

26. Ney M, Vandermeer B, Van Zanten SJV et al. (2013) Meta-Analysis: Oral or enteral nutritional supplementation in cirrhosis. Alimentary Pharmacology and Therapeutics 37:672-679.

27. Puli SR, Reddy JB, Bechtold ML et al. (2009) EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review (Structured abstract). Digestive Diseases and Sciences 54:2330-2337.

28. Cahen DL, Gouma DJ, Laramee P et al. (2011) Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology 141:1690-1695.

29. Villatoro E, Mulla M, and Larvin M. (2010) Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database of Systematic Reviews CD002941.

30. Yao L, Huang X, Li Y et al. (2010) Prophylactic antibiotics reduce pancreatic necrosis in acute necrotizing pancreatitis: a meta-analysis of randomized trials. Digestive Surgery 27:442-449.

31. Petrov MS, Shanbhag S, Chakraborty M et al. (2010) Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 139:813-820.

32. Al-Omran M, Albalawi ZH, Tashkandi MF et al. (2010) Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database of Systematic Reviews CD002837.

33. Petrov MS and Whelan K. (2010) Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. British Journal of Nutrition 103:1287-1295.

34. Wu XM, Ji KQ, Wang HY et al. (2010) Total enteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. Pancreas 39:248-251.

35. Whitfield K, Rambaldi A, Wetterslev J et al. (2009) Pentoxifylline for alcoholic hepatitis. Cochrane Database of Systematic Reviews CD007339.

36. Sidhu SS, Goyal O, Singla M et al. (2012) Pentoxifylline in severe alcoholic hepatitis: a prospective, randomised trial. Journal of the Association of Physicians of India 60:20-22.

37. Cardenas A, Gins P, Marotta P et al. (2012) Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. Journal of Hepatology 56:571-578.

38. Kim MY, Cho MY, Baik SK et al. (2012) Beneficial effects of candesartan, an angiotensin-blocking agent, on compensated alcoholic liver fibrosis - a randomized open-label controlled study. Liver International 32:977-987.

39. Spahr L, Chalandon Y, Terraz S et al. (2013) Autologous bone marrow mononuclear cell transplantation in patients with decompensated alcoholic liver disease: a randomized controlled trial. PLoS ONE [Electronic Resource] 8:e53719.

40. Templeton L, Velleman R, Russell CE-MA et al. (2010) Psychological interventions with families of alcohol misusers: A systematic review. Addiction Research & Theory 18.

41. Saitz R, Cheng DM, Winter M et al. (18-9-2013) Chronic care management for dependence on alcohol and other drugs: the AHEAD randomized trial. JAMA 310:1156-1167.

42. Oslin DW, Lynch KG, Maisto SA et al. (2014) A randomized clinical trial of alcohol care management delivered in Department of Veterans Affairs primary care clinics versus specialty addiction treatment. Journal of General Internal Medicine 29:162-168.

43. Boscolo-Berto R, Viel G, Montisci M et al. (2013) Ethyl glucuronide concentration in hair for detecting heavy drinking and/or abstinence: a meta-analysis. [Review]. International Journal of Legal Medicine 127:611-619.

44. Elholm B, Larsen K, Hornnes N et al. (2011) Alcohol withdrawal syndrome: symptom-triggered versus fixed-schedule treatment in an outpatient setting. Alcohol & Alcoholism 46:318-323.

45. 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 CD006266.

46. 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 30:136-148.

47. Lynch KG, Van HD, Drapkin M et al. (2010) Moderators of response to telephone continuing care for alcoholism. American journal of health behavior 34:788-800.

48. 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 139:217-229.

49. Nordback I, Pelli H, Lappalainen-Lehton R et al. (2009) The Recurrence of Acute Alcohol-Associated Pancreatitis Can Be Reduced: A Randomized Controlled Trial. Gastroenterology 136:848-855.

50. Manning V, Best D, Faulkner N et al. (1-11-2012) Does active referral by a doctor or 12-Step peer improve 12-Step meeting attendance? Results from a pilot randomised control trial. Drug & Alcohol Dependence 126:131-137.

51. Jonas DE, Garbutt JC, Amick HR et al. (6-11-2012) Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. [Review]. Annals of Internal Medicine 157:645-654.

52. Alessi SM and Petry NM. (2013) A randomized study of cellphone technology to reinforce alcohol abstinence in the natural environment. Addiction 108:900-909.

53. Sannibale C, Teesson M, Creamer M et al. (2013) Randomized controlled trial of cognitive behaviour therapy for comorbid post-traumatic stress disorder and alcohol use disorders. Addiction 108:1397-1410.

54. Riper H, Andersson G, Hunter SB et al. (2014) Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: a meta-analysis. Addiction 109:394-406.

55. Dieperink E, Fuller B, Isenhart C et al. (2014) Efficacy of motivational enhancement therapy on alcohol use disorders in patients with chronic hepatitis C: a randomized controlled trial. Addiction 109:1869-1877.

56. Field C, Walters S, Marti CN et al. (2014) A multisite randomized controlled trial of brief intervention to reduce drinking in the trauma care setting: how brief is brief? Annals of Surgery 259:873-880.

57. Signor L, Pierozan PS, Ferigolo M et al. (2013) Efficacy of the telephone-based Brief Motivational Intervention for alcohol problems in Brazil. Revista Brasileira de Psiquiatria 35:254-261.

58. Gustafson DH, McTavish FM, Chih MY et al. (2014) A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry 71:566-572.

59. Lucht MJ, Hoffman L, Haug S et al. (2014) A Surveillance Tool Using Mobile Phone Short Message Service to Reduce Alcohol Consumption Among Alcohol-Dependent Patients. SO: Alcoholism: Clinical and Experimental Research 38:1728-1736.

60. Agyapong VI, Ahern S, McLoughlin DM et al. (10-12-2012) Supportive text messaging for depression and comorbid alcohol use disorder: single-blind randomised trial. Journal of Affective Disorders 141:168-176.

61. Agyapong VI, Milnes J, McLoughlin DM et al. (2013) Perception of patients with alcohol use disorder and comorbid depression about the usefulness of supportive text messages. Technology & Health Care 21:31-39.

62. Agyapong VI, McLoughlin DM, and Farren CK. (2013) Six-months outcomes of a randomised trial of supportive text messaging for depression and comorbid alcohol use disorder. Journal of Affective Disorders 151:100-104.

63. Hester RK, Lenberg KL, Campbell W et al. (2013) Overcoming Addictions, a Web-based application, and SMART Recovery, an online and in-person mutual help group for problem drinkers, part 1: three-month outcomes of a randomized controlled trial. Journal of Medical Internet Research 15:e134.

64. Klauss J, Penido Pinheiro LC, Silva Merlo BL et al. (2014) A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. International Journal of Neuropsychopharmacology 17:1793-1803.

65. Zarkin GAB. (2010) The effect of alcohol treatment on social costs of alcohol dependence: Results from the combine study. Medical Care 48:396-401.

66. Litten RZ, Fertig JB, Falk DE et al. (2012) A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. Alcoholism: Clinical & Experimental Research 36:406-416.

67. 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 & Experimental Research 34:1849-1857.

68. 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.

69. Kranzler HR, Armeli S, Tennen H et al. (2011) A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype.[Erratum appears in J Clin Psychopharmacol. 2011 Oct;31(5):576]. Journal of clinical psychopharmacology 31:22-30.

70. Kranzler HR, Armeli S, and Tennen H. (2012) Post-treatment outcomes in a double-blind, randomized trial of sertraline for alcohol dependence. Alcoholism: Clinical & Experimental Research 36:739-744.

71. 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.[Erratum appears in Am J Psychiatry. 2011 Jul;168(7):756]. American Journal of Psychiatry 168:265-275.

72. lovieno N, Tedeschini E, and Bentley KH. (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 72:1144-1151.

73. Berger L, Fisher M, Brondino M et al. (2013) Efficacy of acamprosate for alcohol dependence in a family medicine setting in the United States: a randomized, double-blind, placebo-controlled study. Alcoholism: Clinical & Experimental Research 37:668-674.

74. Jonas DE, Amick HR, Feltner C et al. (14-5-2014) Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. [Review]. JAMA 311:1889-1900.

75. De SA. (2014) A comparative study using Disulfiram and Naltrexone in alcohol-dependent adolescents. Journal of Substance Use 19:341-345.

76. Pani PP, Trogu E, Pacini M et al. (2014) Anticonvulsants for alcohol dependence. SO: Cochrane Database of Systematic Reviews .

77. Blodgett JC, Del Re AC, Maisel NC et al. (2014) A meta-analysis of topiramate's effects for individuals with alcohol use disorders. Alcoholism: Clinical & Experimental Research 38:1481-1488.

78. Martinotti G, Di Nicola M, De Vita O et al. (2014) Low-dose topiramate in alcohol dependence: a single-blind, placebo-controlled study. Journal of clinical psychopharmacology 34:709-715.

79. Likhitsathian S, Uttawichai K, Booncharoen H et al. (1-12-2013) Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: a 12-week, randomized, placebo-controlled trial. Drug & Alcohol Dependence 133:440-446.

80. Fertig JB, Ryan ML, Falk DE et al. (2012) A double-blind, placebo-controlled trial assessing the efficacy of levetiracetam extended-release in very heavy drinking alcohol-dependent patients. Alcoholism: Clinical & Experimental Research 36:1421-1430.

81. Mason BJ, Quello S, Goodell V et al. (2014) Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Internal Medicine 174:70-77.

82. Book SW, Thomas SE, Smith JP et al. (2013) Treating individuals with social anxiety disorder and at-risk drinking: phasing in a brief alcohol intervention following paroxetine. Journal of Anxiety Disorders 27:252-258.

83. Sherwood BE, Davila D, Nakamura A et al. (2014) A randomized, double-blind, placebo-controlled trial of quetiapine in patients with bipolar disorder, mixed or depressed phase, and alcohol dependence. Alcoholism: Clinical & Experimental Research 38:2113-2118.

84. Kishi T, Sevy S, Chekuri R et al. (2013) Antipsychotics for primary alcohol dependence: a systematic review and meta-analysis of placebo-controlled trials. Journal of Clinical Psychiatry 74:e642-e654.

85. Leggio L, Ferrulli A, Zambon A et al. (2012) Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. Addictive Behaviors 37:561-564.

86. Morley KC, Baillie A, Leung S et al. (2014) Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety. Alcohol & Alcoholism Epub.

87. Manzardo AM, He J, Poje A et al. (1-12-2013) Double-blind, randomized placebo-controlled clinical trial of benfotiamine for severe alcohol dependence. Drug & Alcohol Dependence 133:562-570.

88. Wong CJ, Witcher J, Mallinckrodt C et al. (2014) A phase 2, placebo-controlled study of the opioid receptor antagonist LY2196044 for the treatment of alcohol dependence. Alcoholism: Clinical & Experimental Research 38:511-520.

89. Litten RZ, Ryan ML, Fertig JB et al. (2013) A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. Journal of Addiction Medicine 7:277-286.

90. Brink W, Sorensen P, Torup L et al. (2014) Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. SO: Journal of psychopharmacology (Oxford, England) 28:733-744.

91. Gual A, He Y, Torup L et al. (2013) A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. European Neuropsychopharmacology 23:1432-1442.

92. Mann K, Bladstrom A, Torup L et al. (15-4-2013) Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biological Psychiatry 73:706-713.

93. van den Brink W, Aubin HJ, Bladstrom A et al. (2013) Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies.[Erratum appears in Alcohol Alcohol. 2013 Nov-Dec;48(6):746]. Alcohol & Alcoholism 48:570-578.

94. Laramee P, Brodtkorb TH, Rahhali N et al. (2014) The cost-effectiveness and public health benefit of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: a Markov model. BMJ Open 4:e005376.