NICE National Institute for Health and Care Excellence

Appendix A: Summary of evidence from surveillance

2018 surveillance of Alcohol-use disorders: diagnosis and management of physical complications (2010) NICE guideline CG100

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a final decision on the need to update each section of the guideline.

1.1 Acute alcohol withdrawal

Recommendations in this section of the guideline

1.1.1 Admission to hospital

1.1.1.1 For people in acute alcohol withdrawal with, or who are assessed to be at high risk of developing, alcohol withdrawal seizures or delirium tremens, offer admission to hospital for medically assisted alcohol withdrawal. **[2010]**

1.1.1.2 For young people under 16 years who are in acute alcohol withdrawal, offer admission to hospital for physical and psychosocial assessment, in addition to medically assisted alcohol withdrawal. **[2010]**

1.1.1.3 For certain vulnerable people who are in acute alcohol withdrawal (for example, those who are frail, have cognitive impairment or multiple comorbidities, lack social support, have learning difficulties or are 16 or 17 years), consider a lower threshold for admission to hospital for medically assisted alcohol withdrawal. **[2010]**

1.1.1.4 For people who are alcohol dependent but not admitted to hospital, offer advice to avoid a sudden reduction in alcohol intake[1] and information about how to contact local alcohol support services. **[2010]**

1.1.2 Assessment and monitoring

1.1.2.1 Healthcare professionals who care for people in acute alcohol withdrawal should be skilled in the assessment and monitoring of withdrawal symptoms and signs. **[2010]**

1.1.2.2 Follow locally specified protocols to assess and monitor patients in acute alcohol withdrawal. Consider using a tool (such as the Clinical Institute Withdrawal Assessment – Alcohol, revised [CIWA–Ar] scale[2]) as an adjunct to clinical judgement. **[2010]**

1.1.2.3 People in acute alcohol withdrawal should be assessed immediately on admission to hospital by a healthcare professional skilled in the management of alcohol withdrawal. **[2010]**

1.1.3 Treatment for acute alcohol withdrawal

1.1.3.1 Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal as follows:

- Consider offering a benzodiazepine[3] or carbamazepine[4].
- Clomethiazole[5] may be offered as an alternative to a benzodiazepine or carbamazepine. However, it should be used with caution, in inpatient settings only and according to the summary of product characteristics. **[2010]**

1.1.3.2 People with decompensated liver disease who are being treated for acute alcohol withdrawal should be offered advice from a healthcare professional experienced in the management of patients with liver disease. **[2010]**

1.1.3.3 Offer information about how to contact local alcohol support services to people who are being treated for acute alcohol withdrawal. **[2010]**

1.1.3.4 Follow a symptom-triggered regimen[6] for drug treatment for people in acute alcohol withdrawal who are:

- in hospital **or**
- in other settings where 24-hour assessment and monitoring are available. **[2010]**

1.1.4 Management of delirium tremens

1.1.4.1 In people with delirium tremens, offer oral lorazepam[7] as first-line treatment. If symptoms persist or oral medication is declined, offer parenteral lorazepam[7] or haloperidol[8]. **[2010, amended 2017]**

1.1.4.2 If delirium tremens develops in a person during treatment for acute alcohol withdrawal, review their withdrawal drug regimen. **[2010]**

1.1.5 Management of alcohol withdrawal seizures

1.1.5.1 In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (such as lorazepam[7]) to reduce the likelihood of further seizures. **[2010]**

1.1.5.2 If alcohol withdrawal seizures develop in a person during treatment for acute alcohol withdrawal, review their withdrawal drug regimen. **[2010]**

1.1.5.3 Do not offer phenytoin to treat alcohol withdrawal seizures. **[2010]**

Footnotes

[1] While abstinence is the goal, a sudden reduction in alcohol intake can result in severe withdrawal in dependent drinkers.

[2] Sullivan JT, Sykora K, Schneiderman J et al. (1989) Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). British Journal of Addiction 84:1353-1357.

[3] Benzodiazepines are used in UK clinical practice in the management of alcohol-related withdrawal symptoms. Diazepam and chlordiazepoxide have UK marketing authorisation for the management of acute alcohol withdrawal symptoms. However, at the time of publication (April 2017), alprazolam, clobazam and lorazepam did not have UK marketing authorisations for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. In addition, the summary of product characteristics (SPC) for alprazolam advises that benzodiazepines should be used with extreme caution in patients with a history of alcohol abuse. The SPC for clobazam states that it must not be used in patients with any history of alcohol dependence (due to increased risk of dependence). The SPC for lorazepam advises that use in individuals with a history of alcoholism should be avoided (due to increased risk of dependence).

[4] Although carbamazepine is used in UK clinical practice in the management of alcohol-related withdrawal symptoms, at the time of publication (April 2017), it did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[5] Clomethiazole has a UK marketing authorisation for the treatment of alcohol withdrawal symptoms where close hospital supervision is also provided. However, at the time of publication (April 2017), the SPC advises caution in prescribing clomethiazole for individuals

known to be addiction-prone and to outpatient alcoholics. It also advises against prescribing it to patients who continue to drink or abuse alcohol. Alcohol combined with clomethiazole, particularly in alcoholics with cirrhosis, can lead to fatal respiratory depression even with short-term use. Clomethiazole should only be used in hospital under close supervision or, in exceptional circumstances, on an outpatient basis by specialist units when the daily dosage must be monitored closely.

[6] A symptom-triggered regimen involves treatment tailored to the person's individual needs. These are determined by the severity of withdrawal signs and symptoms. The patient is regularly assessed and monitored, either using clinical experience and questioning alone or with the help of a designated questionnaire such as the CIWA–Ar. Drug treatment is provided if the patient needs it and treatment is withheld if there are no symptoms of withdrawal.

[7] Although lorazepam is used in UK clinical practice in the management of delirium tremens, at the time of publication (April 2017), it did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. In addition, the SPC advises that use in individuals with a history of alcoholism should be avoided (due to increased risk of dependence).

[8] Although haloperidol is used in UK clinical practice in the management of delirium tremens, at the time of publication (April 2017), it did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. In addition, the SPC advises caution in patients suffering from conditions predisposing to convulsions, such as alcohol withdrawal.

Surveillance decision

New evidence has been identified on pharmacotherapies for acute alcohol withdrawal. Recommendation 1.1.3.1 (treatment of acute alcohol withdrawal) needs updating to consider this new evidence.

Editorial amendments

There are no editorial amendments.

2015 surveillance summary

In previous surveillance of this guideline 7 studies were found.

Adjuvant dexmedetomidine (1 RCT)

One RCT which evaluated up to 5 days of dexmedetomidine (DEX) compared to placebo as adjunctive therapy to

lorazepam in a symptom-triggered regimen in people (n=24) with severe alcohol withdrawal indicated that in the short-term (first 24hrs) adjunctive DEX maintains symptom control and reduces lorazepam exposure compared to placebo but not in the long-term (7 days).(1)

Barbiturates (1 RCT)

One RCT (2) indicated that a single dose of intravenous phenobarbital 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.

Symptom-triggered benzodiazepines (2 RCTs)

One RCT (3) 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.

One RCT (4), which compared a fixed tapering dose with a symptom-triggered regimens 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. Both regimens had the same incidence of complications.

Other drugs and therapies (3 RCTs)

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 an RCT (5) in people undergoing alcohol withdrawal (n=108).

One RCT (6) 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 during detoxification (n=42) indicated that while safe this option had no clinical benefit over placebo.

One RCT which compared lorazepam to ethanol/lorazepam for preventing alcohol withdrawal syndrome 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.(7)

2018 surveillance summary

In the 2018 surveillance of this guideline 13 studies were found.

Adjuvant dexmedetomidine (4 studies)

One RCT (8) studying the effect of adding DEX to benzodiazepines for patients with acute withdrawal syndrome (n=72 patients) found that the addition of DEX significantly reduced median cumulative diazepam dose (60mg versus 90mg, $p<0.001$), and significantly fewer patients required haloperidol (2 versus 10, $p=0.02$).

One systematic review (9) of DEX for patients with acute withdrawal syndrome (1 RCT, 7 non-RCTs; number of patients not reported) found that the addition of DEX significantly decreased benzodiazepine requirements compared with placebo in the first 24 hours after initiation compared with the 24 hours prior to initiation (-56.8 mg versus -8 mg; p=

0.037). DEX was also found to reduce tachycardia, and hypertension but not need for ventilation or length of hospital stay.

One systematic review (10) of adjunctive DEX for patients with severe acute alcohol withdrawal syndrome (13 studies) found that that the addition of DEX was well tolerated and associated with a decrease in short-term benzodiazepine requirements after initiation, and improvement in hemodynamic parameters, such as a decrease in blood pressure and heart rate. The authors concluded that adjunctive DEX should be considered in severe alcohol withdrawal syndrome.

One systematic review (11) of DEX adjunctive to benzodiazepines for patients in intensive care (ICU) with alcohol withdrawal delirium (4 studies) found that adjuvant use of DEX with benzodiazepine-based therapy decreased CIWA scores (Weighted Mean Difference 5.2; p <0.0001). The authors concluded that the use of DEX as an adjuvant to benzodiazepine-based therapy decreased delirium more effectively than benzodiazepine-based therapy alone in adult ICU patients experiencing alcohol withdrawal delirium.

Barbiturates (4 studies)

One systematic review (12) of barbiturates for alcohol withdrawal syndrome (15 studies) found that barbiturates provide effective treatment for alcohol withdrawal syndrome in the emergency department and for severe withdrawal in the intensive care unit. However the authors concluded that additional studies are needed.

One systematic review (13) of barbiturates for alcohol withdrawal syndrome (7 studies) found that barbiturates alone or in combination with benzodiazepines are at least as effective and have a similar safety profile as benzodiazepines. The authors concluded that adding phenobarbital to benzodiazepine-based regimen may be particularly useful in patients with benzodiazepine-refractory alcohol withdrawal syndrome.

One systematic review (14) studying the effects of phenobarbital use with and without benzodiazepines for acute alcohol withdrawal (n=4 trials and 5 observational studies; n=720 patients) found that phenobarbital alone or in combination with benzodiazepines may provide similar or improved outcomes when compared with alternative therapies, including benzodiazepines alone.

One systematic review (15) looking at treatments for severe alcohol withdrawal (27 studies) found that benzodiazepines, in combination with phenobarbital, may reduce the need for mechanical ventilation and lead to shorter intensive care unit stays. However the authors found that severe alcohol withdrawal is poorly defined and there is limited data available and more prospective randomised studies are needed.

Baclofen (1 Cochrane review)

One Cochrane review (16) of baclofen for severe alcohol withdrawal syndrome (3 RCTs; n=141 patients) found that for the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) scores there was no significant difference with baclofen compared with diazepam, placebo, or chlordiazepoxide, but the quality of the evidence was poor.

Other drugs and therapies (4 studies)

One systematic review (17) of acupuncture (in addition to pharmacotherapy) for alcohol withdrawal syndrome (11 RCTS; n=875 participants) found that there was no significant difference between acupuncture and sham acupuncture for craving for alcohol among participants with acute alcohol withdrawal, and no difference in completion rates.

One systematic review (18) of Gamma-hydroxybutyrate (GHB) for alcohol withdrawal syndrome (5 studies) found that GHB may be effective in reducing symptoms of alcohol withdrawal syndrome and produces beneficial effects comparable to those of benzodiazepines or chlometiazole. The authors noted that there were some safety concerns, such as insufficiency against hallucinations and potential development of GHB dependence, which required further study.

One RCT (19) of lorazepam (8mg/day) versus chlordiazepoxide (80 mg/day) for alcohol withdrawal symptoms (n=60 patients) found that there was no significant difference between lorazepam or chlordiazepoxide in reducing alcohol withdrawal symptoms as measured by CIWA-Ar at 8 and 12 days. There was also no difference in liver function tests.

One RCT (20) of parenteral benzodiazepine administered in increasing bolus vs continuous infusion in the treatment of alcohol withdrawal syndrome (n=96 patients) found that there were therapeutic differences associated with bolus diazepam, compared with continuous infusion, in patients with alcohol withdrawal, but no differences in length of hospital stay.

Intelligence gathering

Topic experts indicated that there have been developments in clinical practice over the last 8 years. In particular, there has been further research into pharmacotherapy for acute withdrawal. The role of baclofen has not been covered in the guideline and the use of disulfiram could be reviewed further as it is still in use despite it being discouraged. Similarly, the role of carbamazepine for alcohol detox might need considering. Topic experts also highlighted that symptom-triggered alcohol detox regimens may not be optimal, resulting in adverse complications. However, evidence currently supports symptom-triggered regimens.

Impact statement

A total of 20 studies looking at pharmacotherapy for acute alcohol withdrawal were found covering adjuvant dexmedetomidine, adjuvant barbiturates, baclofen, symptom-triggered lorazepam and several other therapies.

Adjuvant dexmedetomidine

Evidence on adjuvant dexmedetomidine (3 systematic reviews and 2 RCTs) indicated that it may be helpful in decreasing benzodiazepine usage during acute withdrawal. However, there was no change in hospital stay or need for ventilation. Currently adjuvant dexmedetomidine is not mentioned in recommendation 1.1.3.1 (treatment for acute alcohol withdrawal). As such, this new evidence has the potential to impact upon this recommendation.

Barbiturates

Evidence on barbiturates (4 systematic reviews and 1 RCT) indicated that they may be effective in managing acute withdrawal, in particular when a patient is refractory to benzodiazepines. There was also evidence that benzodiazepines, in combination with phenobarbital, may reduce the need for mechanical ventilation and lead to shorter intensive care unit stays. Currently barbiturates are not mentioned in recommendation 1.1.3.1. As such, this new evidence has the potential to impact upon this recommendation.

Symptom-triggered lorazepam

Evidence on symptom-triggered lorazepam (2 RCTs) indicates it is as effective as fixed dose lorazepam but with significantly shorter length of treatment and lower doses of lorazepam. This is in line with current recommendation 1.1.3.4.

Baclofen and other therapies

One Cochrane review of baclofen found that it may be as effective as benzodiazepines in managing acute alcohol withdrawal but that the evidence base was weak. Evidence on other therapies including RCTs of GHB, acupuncture, chlordiazepoxide, and bolus benzodiazepines found evidence of little difference and study sample sizes were generally small. Given this it is uncertain if these studies would change current guideline recommendations.

Summary

Given that recommendation 1.1.3.1 will need updating for adjuvant dexmedetomidine and barbiturates, it would seem prudent to undertake a review of all pharmacotherapies for acute alcohol withdrawal and provide a more complete picture of which are the most effective and cost-effective pharmacotherapies for acute alcohol withdrawal. This piece of work would be in agreement with topic experts who indicated that there is a need to review pharmacotherapies for acute alcohol withdrawal.

New evidence identified that may change current recommendations.

1.2 Wernicke's encephalopathy

Recommendations in this section of the guideline

1.2.1.1 Offer 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. It should be given orally or parenterally as described in recommendations 1.2.1.2 to 1.2.1.4. **[2010]**

1.2.1.2 Offer prophylactic oral thiamine to harmful or dependent drinkers:

- if they are malnourished or at risk of malnourishment **or**

- if they have decompensated liver disease **or**
- if they are in acute withdrawal **or**
- before and during a planned medically assisted alcohol withdrawal. **[2010]**

1.2.1.3 Offer prophylactic parenteral thiamine followed by oral thiamine to harmful or dependent drinkers:

- if they are malnourished or at risk of malnourishment **or**
- if they have decompensated liver disease

and in addition

- they attend an emergency department **or**
- are admitted to hospital with an acute illness or injury. **[2010]**

1.2.1.4 Offer parenteral thiamine to people with suspected Wernicke's encephalopathy. Maintain a high level of suspicion for the possibility of Wernicke's encephalopathy, particularly if the person is intoxicated. Parenteral treatment should be given for a minimum of 5 days, unless Wernicke's encephalopathy is excluded. Oral thiamine treatment should follow parenteral therapy. **[2010]**

Surveillance decision

This section of the guideline should not be updated.

Editorial amendments

Clarification is needed on the wording on doses of thiamine and the use of oral or parenteral thiamine. This refresh will be undertaken by committee.

2015 surveillance summary

In previous surveillance of this guideline, an update of a Cochrane review (21) on thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol was identified (2 studies). The review found limited evidence that higher dose thiamine (20mg/day) had better outcomes than lower doses (5mg/day) but concluded that there is insufficient evidence to guide clinical practice.

2018 surveillance summary

One systematic review (22) was identified which considered the management of alcohol-associated vitamin and electrolyte deficiency (unclear number of included studies). The review concluded that IV thiamine supplementation should be used for the prevention and management of Wernicke's encephalopathy, in place of the 'banana bag' method.

Intelligence gathering

Topic expert feedback indicated that there is a discrepancy between the British National Formulary (BNF), Summary of Product Characteristics (SPC) and NICE with the management of thiamine for patients with possible Wernicke's encephalopathy. Clinical advice on this matter agreed that there was a discrepancy that should be reviewed by committee for clarity and resolution. There may also be uncertainty around the use of parenteral products and a need to advise on MHRA safety warnings on parenteral thiamine.

Impact statement

One Cochrane review was identified which indicated that IV thiamine supplementation should be used for the prevention and management of Wernicke's encephalopathy, compared with the banana bag method. One Cochrane review found insufficient evidence for the prevention and treatment of Wernicke-Korsakoff Syndrome. This evidence does not impact on current recommendations. However, topic experts and clinical advice indicated that there is a need to clarify wording around thiamine doses and oral or parenteral usage. This refresh will be undertaken by committee to ensure the wording is clinically meaningful and appropriate.

New evidence is unlikely to change guideline recommendations

1.3 Alcohol-related liver disease

Recommendations in this section of the guideline

1.3.1 Assessment and diagnosis of alcohol-related liver disease

1.3.1.1 Exclude alternative causes of liver disease in people with a history of harmful or hazardous drinking who have abnormal liver blood test results. **[2010]**

1.3.1.2 Refer people to a specialist experienced in the management of alcohol-related liver disease to confirm a clinical diagnosis of alcohol-related liver disease. **[2010]**

1.3.1.3 Consider liver biopsy for the investigation of alcohol-related liver disease. **[2010]**

1.3.1.4 When considering liver biopsy for the investigation of alcohol-related liver disease:

- take into account the small but definite risks of morbidity and mortality
- discuss the benefits and risks with the patient **and**
- ensure informed consent is obtained. **[2010]**

1.3.1.5 In people with suspected acute alcohol-related hepatitis, consider a liver biopsy to confirm the diagnosis if the hepatitis is severe enough to require corticosteroid treatment. **[2010]**

1.3.2 Referral for consideration of liver transplantation

1.3.2.1 Refer patients with decompensated liver disease to be considered for assessment for liver transplantation if they:

- still have decompensated liver disease after best management and 3 months' abstinence from alcohol **and**
- are otherwise suitable candidates for liver transplantation. **[2010, amended 2017]**

1.3.3 Corticosteroid treatment for alcohol-related hepatitis

1.3.3.1 Offer corticosteroid[9] treatment to people with severe alcohol-related hepatitis and a discriminant function[10] of 32 or more, only after:

- effectively treating any active infection or gastrointestinal bleeding that may be present
- controlling any renal impairment
- discussing the potential benefits and risks with the person and their family members or carers (as appropriate), explaining that corticosteroid treatment:
    - has been shown to improve survival in the short-term (1 month)
    - has not been shown to improve survival over a longer term (3 months to 1 year)
    - has been shown to increase the risk of serious infections within the first 3 months of starting treatment. **[2017]**

1.3.4 Nutritional support for alcohol-related hepatitis

1.3.4.1 Assess the nutritional requirements of people with acute alcohol-related hepatitis. Offer nutritional support if needed[11] and consider using nasogastric tube feeding. **[2010]**

Footnotes

[9] Corticosteroids are used in UK clinical practice in the management of severe alcohol-related hepatitis. At the time of publication (April 2017), prednisolone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[10] Maddrey's discriminant function (DF) was described to predict prognosis in alcohol-related hepatitis and identify patients suitable for treatment with steroids. It is 4.6 x [prothrombin time – control time (seconds)] + bilirubin in mg/dl. To calculate the DF using bilirubin in micromol/l divide the bilirubin value by 17.

[11] See Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE guideline CG32 (2006).

Surveillance decision

This section of the guideline should not be updated.

Editorial amendments

An editorial amendment will be added to direct people to the Cirrhosis in over 16s: assessment and management (NICE guideline NG50) guideline for further information on diagnosing, monitoring and managing cirrhosis.

2015 surveillance summary

In previous surveillance of this guideline 12 relevant studies were identified.

Assessment and diagnosis of alcohol-related liver disease (2 studies)

A systematic review and economic evaluation (23) 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 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.

A systematic review and meta-analysis (24) of diagnostic accuracy studies comparing FibroScan and aspartate transaminase to platelet ratio index (APRI) with liver biopsy for hepatic fibrosis which included 23 studies for FibroScan and 20 studies for APRI was identified. 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 have alcohol dependence or had harmful drinking.

Pharmacological interventions for alcohol-related hepatitis (5 studies)

An RCT (25) 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). 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.

One RCT (26) 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.

One systematic review (27) (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 people with severe alcoholic hepatitis. However, trials of pentoxifylline versus corticosteroid, or as combination therapy did not indicate any difference in reported outcomes.

One RCT (28) 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. 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 been higher in those treated with metadoxine.

One RCT (29) 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.

Nutritional interventions (4 studies)

A meta-analysis (30) (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. However, encephalopathy showed an improvement or resolution with nutritional supplementation.

One RCT (31) 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.

A Cochrane review (32) (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. The review reported significant effects for 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. No overall effect of the supplements on mortality in medical patients was observed.

A systematic review and meta-analysis (33) 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.

Alcohol abstinence (1 study)

A systematic review and meta-analysis (34) including 7 cohort studies which examined the effect of abstinence from alcohol on survival of patients with alcoholic cirrhosis was identified. 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.

2016 exceptional review

An exceptional review was undertaken in 2016 due to the publication of the STOPAH trial. This warranted a partial update of recommendations around corticosteroids. See the 2016 surveillance report for further details.

2018 surveillance summary

In the 2018 surveillance of this guideline 16 studies were identified.

Assessment and diagnosis of alcohol-related liver disease (3 studies)

One Cochrane review (35) of transient elastography for the diagnosis and staging of hepatic fibrosis and cirrhosis in people with alcohol-related liver disease (14 studies; n=834 patients) found that transient elastography may be used as a diagnostic method to rule out liver cirrhosis (F4) in people with alcohol-related liver disease when the pre-test probability is about 51% (range 15% to 79%). Transient elastography may also aid in ruling out severe fibrosis (F3 or worse). The best cut-off values for hepatic fibrosis in people with alcoholic liver disease could not be established yet.

One meta-analysis (36) of individual patient data of diagnosing liver fibrosis with transient elastography (n=10 studies; n=1026 patients) found that there is a link between liver stiffness and the histological features of asymptomatic and non-severe alcoholic hepatitis. The authors concluded that FibroScan assessments of liver fibrosis should take into account aspartate aminotransferase and bilirubin concentrations through the use of specifically adjusted liver stiffness cut-offs for diagnosing alcohol-related liver disease.

One Cochrane review (37) of ultrasonography for the diagnosis of alcohol-related cirrhosis in people with alcoholic liver disease (2 studies; n=205 patients) found that the accuracy of ultrasonography in the 2 included studies was not informative enough to be used as a diagnostic tool for liver cirrhosis in people with alcoholic liver disease. The authors concluded that further research is needed.

Pharmacological interventions for alcohol-related hepatitis (7 studies)

One systematic review (38) of corticosteroids with or without pentoxifylline in patients with severe alcohol-related hepatitis (25 studies; n=2639 patients) found that corticosteroid monotherapy reduced 1-month mortality compared with placebo (OR 0.58; p=0.04), but pentoxifylline monotherapy did not. The mortality with dual corticosteroids plus pentoxifylline was not significant (OR 0.91; p=0.63). However, dual therapy decreased the incidences of hepatorenal syndrome or acute kidney injury (OR 0.47; p=0.01) and the infection risk (OR 0.63; p=0.04) significantly more than corticosteroid monotherapy did. None of the treatments conferred any medium-

term or long-term survival benefits in the present study.

One systematic review (39) of corticosteroids versus pentoxifylline for severe alcohol-related hepatitis (14 RCTs) found that corticosteroids reduced 28-day mortality, compared with placebo (RR 0.53; p=0.006). There was no statistically significant difference in short-term mortality with pentoxifylline, compared with placebo. The incidence of hepatorenal syndrome or sepsis was not impacted by corticosteroids nor pentoxifylline.

One RCT (40) of corticosteroids versus pentoxifylline for severe alcohol-related hepatitis (n=121 patients) found that the 1-month survival rate of patients receiving pentoxifylline was 75.8% compared with 88.1% in those taking prednisolone (p=0.08). The 6-month survival rate was not significantly different between the pentoxifylline and prednisolone groups (64.5% versus 72.9%; p=0.23). Hepatitis complications, including hepatorenal syndrome and side effects, such as infection and gastrointestinal bleeding were similar in the 2 groups.

One systematic review (41) of pharmacotherapy for severe alcohol-related hepatitis (22 trials; n=2621 patients) found that in a network meta-analysis the following interventions decreased the risk of short-term mortality: corticosteroids alone (RR 0.54; 95% CrI 0.39-0.73); corticosteroids in combination with pentoxifylline (RR 0.53; 95% CrI 0.36-0.78); corticosteroids plus N-acetylcysteine (RR 0.15; 95% CI 0.05-0.39); or pentoxifylline alone (RR, 0.70; 95% CrI 0.50-0.97). No treatment was effective in reducing medium-term mortality.

One Cochrane review (42) of pharmacological interventions for alcohol-related liver disease (81 RCTs) found that the effectiveness of any pharmacological intervention versus no intervention in people with alcohol-related hepatitis or severe alcohol-related hepatitis is uncertain. However, propylthiouracil may decrease mortality in people with other alcohol-related liver diseases (OR 2.09, 95% CI 1.12 to 3.90; 226 participants; 1 trial; low-quality evidence), but this needs to be confirmed in further trials.

One RCT (43) (n=70 patients) of prednisone (40 mg/day) versus prednisone (40 mg/day) plus metadoxine tablets (500 mg 3 times daily) in patients with severe alcohol-related hepatitis found that the addition of metadoxine, significantly improved survival at 30 days (74.3 vs. 45.7%, p=0.02), survival at 90 days (68.6 vs. 20.0%; p=0.0001), and there was less development or progression of encephalopathy (28.6 vs. 60.0%, p=0.008) and hepatorenal syndrome (31.4 vs. 54.3%, p=0.05). The incidence of adverse events was similar in both groups.

One RCT (44) of extracorporeal cellular therapy (ELAD) versus standard of care therapy for patients with severe alcohol-related hepatitis (n=203 patients) found that there was no difference in overall survival and the trial failed to meet its primary and secondary end-points.

Corticosteroids for alcohol-related liver disease (3 studies)

One Cochrane review (45) of glucocorticosteroids in people with alcohol-related liver disease (15 trials; n=1861 patients) found that there was no evidence of an effect of glucocorticosteroids on all-cause mortality

up to 3 months following randomisation with random-effects meta-analysis (RR 0.90; 95% CI 0.70 to 1.15) or with Trial Sequential Analysis. There was also no evidence of an effect on health-related quality of life up to 3 months or the occurrence of serious adverse events during treatment.

One systematic review (46) of corticosteroids in patients with severe alcohol-related hepatitis (12 trials; n=1062 patients) found that the occurrence of fungal infections was higher among steroid-treated patients, compared with non-steroid-treated patients (8 versus 1 patient; p=0.02), of which 3 patients died in the corticosteroid arm. However, steroids provided a mortality benefit at 28 days (OR 0.55; 95%CI 0.34-0.90) mainly for liver failure-related death (OR 0.46; 95% CI 0.24-0.87) without differences on mortality from infection or gastrointestinal bleeding.

One analysis (47) of the STOPAH trial (n=1068 patients) found that the 3 newer static scores (Glasgow alcoholic hepatitis score (GAHS); the age, serum bilirubin, international normalized ratio and serum creatinine (ABIC) score; and the model of end-stage liver disease (MELD)) were shown to be superior to discriminant function (DF) for predicting patients likely to benefit from prednisolone up to 90 days. ABIC and GAHS may also identify patients who had a survival benefit 28 days after starting prednisolone treatment.

Nutritional interventions (3 studies)

One systematic review (48) of nutritional therapy in cirrhosis or alcohol-related hepatitis (13 trials) found that nutritional therapy reduced mortality (RR 0.80; 95% CI 0.64 to 0.99) and prevented overt hepatic encephalopathy (RR 0.73; 95% CI 0.55 to 0.96) and infection (RR 0.66; 95% CI 0.45 to 0.98), but the results were not confirmed in random-effects analyses.

One RCT (49) of combination corticosteroids and intensive enteral nutrition therapy versus corticosteroid therapy alone in patients with severe alcohol-related hepatitis (n=136) found no significant difference between groups in 6-month cumulative mortality (p=0.406). The enteral feeding tube was withdrawn prematurely from 48.5% of patients, and serious enteral nutrition related adverse events occurred in 5 patients. Regardless of group, a greater proportion of patients with a daily calorie intake less than 21.5 kcal/kg/day died (65.8%) than patients with a higher intake of calories (65.8% versus 33.1%; p<0.001).

One RCT (50) of probiotics versus placebo for the treatment of alcohol-related hepatitis (n=117 patients) found that 7 days of absence from alcohol and cultured lactobacillus subtilis/Streptococcus faecium (1500 mg/day) was associated with restoration of bowel flora and improvement of lipopolysaccharide (LPS) in patients with alcohol-related hepatitis. However, abstinence from alcohol was deemed to be the most important treatment for patients with alcohol-related abstinence.

Intelligence gathering

Topic experts indicated that Cirrhosis in over 16s: assessment and management (NICE guideline NG50) as being of relevance to the alcohol guideline. As such an editorial amendment will be added to the alcohol guideline to ensure it directs readers to the cirrhosis guideline, for

information. Experts also highlighted the EASL Clinical Practice Guideline on alcohol-related liver disease.

Clinical expert advice was sought on the issue of the analysis (47) of the STOPAH trial in relation to discriminant scores for identifying people likely to benefit from corticosteroids. Feedback indicated that discriminant scores are well established in clinical practice and the SROPAH trial is not strong enough evidence to change clinical practice at this time.

Impact statement

Diagnosis

Five reviews of diagnostic studies were found. Three reviews of transient elastography found that the technology may have a role in diagnosing fibrosis but cut-off values are unclear. One review assessing the role of ultrasonography concluded that the evidence base was not informative enough to be used as a diagnostic tool for liver cirrhosis in people with alcoholic liver disease. Two reviews covering FibroTest, FibroScan, FibroMAX, ELF, and APRI were limited and described as not robust with regards to individuals with alcohol-related liver disease. This evidence is not deemed sufficient to change current recommendations within section 1.3.1.

New evidence is unlikely to change guideline recommendations.

Pharmacological interventions

There were 12 studies of pharmacological interventions. Seven studies evaluating pentoxifylline found mixed effects, with some studies finding a short-term survival benefit and some studies showing no short-term survival benefit. No studies found a medium survival benefit. One network meta-analysis found N-acetylcysteine in combination with corticosteroids to be the most effective therapy for improving short-term survival, one RCT found no survival benefit. One RCT found that propylthiouracil may be effective in improving short-term mortality, but the trial was limited in size (70 patients), and further research is warranted. One study of ELAD found no effects. One RCT of adjunctive metadoxine found improved 60 and 90 day survival. Overall, the evidence base of pharmacological interventions alone or in combination with corticosteroids is mixed and uncertain, and as such there is no anticipated impact on recommendations.

New evidence is unlikely to change guideline recommendations.

Glucocorticosteroids

There were 2 studies of glucocorticosteroids, which found a survival benefit up to 1 month but not at 3 months or longer. The evidence is in line with current recommendation 1.3.3.1 and this recommendation was updated in 2017 based on the STOPAH trial. One analysis of the STOPAH trial indicated that GAHS, ABIC, and MELD may be superior to DF for predicting patients likely to benefit from prednisolone. Currently recommendation 1.3.3.1 only mentions DF. However, clinical feedback indicates that the STOPAH trial is currently not strong enough evidence to change such well established clinical practice and further evidence is needed.

New evidence is unlikely to change guideline recommendations.

Nutritional therapy

There were 7 studies of nutritional therapy. The new evidence is in line with the previous reviewed studies reported in the guideline. As such the new evidence 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. Evidence on probiotics is deemed too immature to impact upon current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

1.4 Alcohol-related pancreatitis

Recommendations in this section of the guideline

1.4.1 Diagnosis of chronic alcohol-related pancreatitis

1.4.1.1 To inform a diagnosis of chronic alcohol-related pancreatitis use a combination of:

- the person's symptoms
- an imaging modality to determine pancreatic structure **and**
- tests of pancreatic exocrine and endocrine function. **[2010]**

1.4.1.2 Use computed tomography as the first-line imaging modality for the diagnosis of chronic alcohol-related pancreatitis in people with a history and symptoms suggestive of chronic alcohol-related pancreatitis. **[2010]**

1.4.2 Pancreatic surgery versus endoscopic therapy for chronic alcohol-related pancreatitis

1.4.2.1 Refer people with pain from chronic alcohol-related pancreatitis to a specialist centre for multidisciplinary assessment. **[2010]**

1.4.2.2 Offer surgery, in preference to endoscopic therapy, to people with pain from large-duct (obstructive) chronic alcohol-related pancreatitis. **[2010]**

1.4.2.3 Offer coeliac axis block, splanchnicectomy or surgery to people with poorly controlled pain from small-duct (non-obstructive) chronic alcohol-related pancreatitis. **[2010]**

1.4.3 Prophylactic antibiotics for acute alcohol-related pancreatitis

1.4.3.1 Do not give prophylactic antibiotics to people with mild acute alcohol-related pancreatitis, unless otherwise indicated. **[2010]**

1.4.4 Nutritional support for acute alcohol-related pancreatitis

1.4.4.1 Offer nutritional support[11] to people with acute alcohol-related pancreatitis:

- early (on diagnosis) **and**
- by enteral tube feeding rather than parenterally where possible. **[2010]**

1.4.5 Enzyme supplementation for chronic alcohol-related pancreatitis

1.4.5.1 Offer pancreatic enzyme supplements to people with chronic alcohol-related pancreatitis who have symptoms of steatorrhoea or poor nutritional status due to exocrine pancreatic insufficiency. **[2010]**

1.4.5.2 Do not prescribe pancreatic enzyme supplements to people with chronic alcohol-related pancreatitis if pain is their only symptom. **[2010]**

Surveillance decision

This section of the guideline should not be updated.

Editorial amendments

Overlaps were identified between this section of alcohol-use disorders: diagnosis and management of physical complications (NICE guideline CG100) and pancreatitis (NICE guideline NG104). The following editorial amendments are proposed to manage the overlap:

- Withdraw 1.4.2.2 from CG100 and incorporate pancreatitis guideline recommendation 1.3.8
- Withdraw 1.4.3.1 from CG100 and incorporate pancreatitis guideline recommendation 1.2.3
- Withdraw 1.4.4.1 from CG100 and incorporate pancreatitis guideline recommendations 1.2.5 to 1.2.7.

2015 surveillance summary

No relevant evidence was identified.

2018 surveillance summary

No relevant evidence was identified.

Intelligence gathering

Topic expert feedback indicated that the recent pancreatitis NICE guideline (NG104) overlaps with the current guideline and has a more recent evidence base. Experts also highlighted the NCEPOD pancreatitis report practice guideline.

Impact statement

Three studies were identified, which indicate that the benefits of nutritional supplements may be limited to certain outcomes. This does not impact on current guideline recommendations. However, amendments to CG100 are needed to ensure it links to the more recent recommendation (based on recent evidence) presented in the pancreatitis

NICE guideline (NG104). This refresh will be managed as an editorial amendment, as outlined above.	New evidence is unlikely to change guideline recommendation

Research recommendations

Acute alcohol withdrawal

RR1. What is the clinical and cost-effectiveness of admitting people who attend hospital in mild or moderate acute alcohol withdrawal for unplanned medically assisted alcohol withdrawal compared with no admission and a planned medically assisted alcohol withdrawal with regard to the outcome of long-term abstinence?

RR2 What is the efficacy and cost-effectiveness of clomethiazole compared with chlordiazepoxide or carbamazepine or benzodiazepines for the treatment of acute alcohol withdrawal with regard to the outcomes of withdrawal severity, risk of seizures, risk of delirium tremens, length of treatment and patient satisfaction?

RR3. What is the clinical and cost-effectiveness of interventions delivered in an acute hospital setting by an alcohol specialist nurse compared to those managed through acute care setting with no input from an alcohol nurse specialist?

Summary of findings

No new evidence that directly answered these research recommendation was found and no ongoing studies were identified.

Surveillance decision

These research recommendations will be considered again at the next surveillance point.

Wernicke's encephalopathy

RR4. What is the clinical and cost-effectiveness of the use of parenteral versus oral thiamine in preventing the first onset of Wernicke's encephalopathy in people undergoing medically assisted alcohol withdrawal?

Summary of findings

No new evidence that answered this research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

Alcohol-related liver disease

RR5 What is the cost-effectiveness of the use of liver biopsy in addition to laboratory and clinical markers for the diagnosis of alcohol-related liver disease or alcohol-related hepatitis in patients with suspected alcohol-related liver disease?

RR6 What is the clinical and cost-effectiveness of enteral nutritional support versus normal diet to improve survival in patients with acute severe alcohol-related hepatitis?

Summary of findings

No new evidence that directly answered these research recommendations was found and no ongoing studies were identified.

Surveillance decision

These research recommendations will be considered again at the next surveillance point.

Alcohol-related pancreatitis

RR7 What is the clinical and cost-effectiveness of nasogastric versus nasojejunal delivery of nutritional support to patients with acute severe alcohol-related pancreatitis?

Summary of findings

No new evidence that answered this research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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