The National Clinical Guideline Centre

for acute and chronic conditions

Funded to produce guidelines for the NHS by NICE

ALCOHOL USE DISORDERS: DIAGNOSIS AND CLINICAL MANAGEMENT OF ALCOHOL-RELATED PHYSICAL COMPLICATIONS

Royal College of Physicians

Setting higher medical standards

Contents

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- Member of the trial management group for a study funded by NIHR-HTA: STOPAH (steroids or pentoxifylline in alcoholic hepatitis).

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Dr Annabelle Bundle
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Dr Anne McCune
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Dr Marsha Morgan
- Paid member of the advisory board of the Institute of Alcohol Studies.

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Dr Stephen Pereira
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Mr Colin Standfield
- Received honorarium as Chair of the Ealing and West London Research Ethics Committee

Professor Robin Touquet
- Investigator of the Paddington Alcohol Test since 1996
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1.1 GLOSSARY OF TERMS

The Department of Health recently revised the way in which it describes drinking behaviours; 'hazardous drinkers' are now described as being at increased risk and 'harmful drinkers' are now described as being at higher risk. Due to the extensive use of the terms hazardous and harmful drinking within the scientific literature, the World Health Organization International Classification of Diseases (10th revision), and many of the tools recommended in this guideline, the committee agreed that it would be helpful for methodological reasons and clarity within the clinical field to retain the terms hazardous and harmful drinking.

Abstinence
Never drinking alcohol. People who do not drink alcohol can be described as 'abstainers', 'total abstainers' or 'teetotallers'.

Acute alcohol withdrawal
The physical symptoms someone can experience when they suddenly reduce the amount of alcohol they drink if they have previously been drinking excessively for prolonged periods of time.

Alcohol
Ethanol (ethyl alcohol) is the main psychoactive ingredient in alcoholic drinks. By extension, the term 'alcohol' can be used interchangeably with ethanol, and to describe an alcoholic drink.

Alcohol dependence (condition)
A cluster of behavioural, cognitive and physiological factors that typically include a strong desire to drink alcohol and difficulties in controlling its use. Someone who is alcohol-dependent will keep drinking, despite harmful consequences. They will also give alcohol a higher priority than other activities and obligations. Please refer to 'Diagnostic and statistical manual of mental disorders' (DSM-IV) (American Psychiatric Association 2000) and 'International statistical classification of diseases and related health problems – 10th revision' (ICD-10) (World Health Organization 2007).

Alcohol use disorders
Alcohol use disorders cover a wide range of mental health problems recognised within the international disease classification systems (ICD-10, DSM-IV). These include hazardous and harmful drinking and alcohol dependence. See Harmful drinking, Hazardous drinking and Alcohol dependence.

Alcohol Use Disorders Identification Test (AUDIT)
AUDIT is an alcohol screening test designed to detect whether people are drinking harmful or hazardous amounts of alcohol. It can also be used to identify people who warrant further diagnostic tests for alcohol dependence.

Alcohol-related harm
Physical or mental harm caused either entirely or partly by alcohol. If it is entirely as a result of alcohol, it is known as 'alcohol-specific'. If it is only partly caused by alcohol it is described as 'alcohol-attributable'.

Assisted withdrawal
See medically assisted withdrawal.

Binge drinking
A heavy drinking session in which someone drinks at least twice the maximum recommended units of alcohol per day in one session.

Blood alcohol concentration (BAC)
Blood alcohol concentration is the concentration of alcohol in the blood. In the UK, BAC is reported in milligrams of alcohol per 100 ml of blood (for example, 80 mg per 100 ml).

Brief intervention
Brief advice or counselling to help someone reduce their alcohol consumption. It can be carried out by members of staff who are not alcohol specialists.

CIWA-Ar
The Clinical Institute Withdrawal Assessment (CIWA-Ar) scale is a validated 10-item assessment tool that can be used to quantify the severity of the alcohol withdrawal syndrome, and to monitor and medicate patients throughout withdrawal.

CIWA-Ad
The CIWA-Ad is an 8-item version of the CIWA-Ar.

Clinical management of people with alcohol-related problems
Any pharmacological or psychosocial intervention carried out by a clinician to manage the clinical problems caused by alcohol or any related medical or psychiatric complications. For example, support to help with withdrawal, managing liver damage and treating conditions such as Wernicke's encephalopathy.

Clinically significant improvement
Some trials define a dichotomous outcome of clinically significant pain relief as having been achieved above a specific threshold on a pain score, e.g. pain. However, there is no standard threshold and each such trial should be considered individually.

Cochrane review
The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).

Cohort study
A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Commissioning
Primary care trusts (PCTs) and drug and alcohol action teams (DAATs) may commission alcohol support services to meet patients' needs from a range of 'providers'. This includes GPs, hospitals, mental health trusts and voluntary and private organisations.

Confidence interval (CI)
A range of values which contain the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Cost-consequence analysis
A type of economic evaluation where, for each intervention, various health outcomes are reported in addition to cost, but there is no overall measure of health gain.

Cost-effectiveness analysis
An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-utility analysis
A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life-years (QALYs).

Dependence
See 'Alcohol dependence'.

Medically assisted alcohol withdrawal
Deliberate withdrawal from alcohol by a dependent drinker under the supervision of medical staff. Prescribed medication may be needed to relieve the symptoms. It can be carried out at home or in a hospital or other inpatient facility.

Harmful drinking
A pattern of drinking alcohol that causes harm to a person's health or wellbeing. The harm may be physical, psychological or social.

Hazardous drinking
A pattern of drinking alcohol that increases the risk of harmful consequences for the person.

Incremental cost
The cost of one alternative less the cost of another.

Incremental cost–effectiveness ratio (ICER)
The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

Intoxication
A state of functional impairment caused by alcohol. For some people this can occur after drinking only a small amount.

Meta-analysis
A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.

Methodological limitations
Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Multivariate analysis
Analysis of more than one variable at a time. Takes into account the effects of all variables on the response of interest.

Observational study
Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.

Odds ratio
A measure of treatment effectiveness: the odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

p values
The probability that an observed difference could have occurred by chance. A p value of less than 0.05 is conventionally considered to be 'statistically significant'.

Quality-adjusted life-year (QALY)
A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.

Quality of life (QoL)
Refers to the level of comfort, enjoyment and ability to pursue daily activities.

Randomised controlled trial (RCT)
A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. Such trial designs help minimise experimental bias.

Sensitivity analysis

A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.

Stakeholder
Any national organisation, including patient and carer groups, healthcare professionals and commercial companies with an interest in the guideline under development.

Statistical significance
A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).

Systematic review
Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Technology appraisal
Formal ascertainment and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.

Treatment
A programme designed to reduce alcohol misuse or dependence or related problems. It could involve a mix of counselling, a medical intervention or advice and the provision of information. Another term for a treatment is an intervention.

UK drinking guidelines
Guidelines set by the UK government on how much alcohol may be consumed without a serious impact on health. The guidelines recommend that men should not regularly drink more than 3–4 units of alcohol per day, and women should not regularly drink more than 2–3 units of alcohol per day. Both are recommended to have some alcohol-free days. In terms of weekly limits, men are advised to drink no more than 21 units and women no more than 14 units per week. Anyone who has drunk heavily in one session is advised to go without alcohol for 48 hours, to give their liver and other body tissues time to recover. See 'Unit'.

Unit
In the UK, alcoholic drinks are measured in units. Each unit corresponds to approximately 8 g or 10 ml of ethanol. The same volume of similar types of alcohol (for example, two pints of lager) can comprise a different number of units depending on the drink's strength (that is, its percentage concentration of alcohol).

Univariate
Analysis which separately explores each variable in a data set.

Utility
A number between 0 and 1 that can be assigned to a particular state of health, assessing the holistic impact on quality of life and allowing states to be ranked in order of (average) patient preference.

Withdrawal

Withdrawal from alcohol. Also see Acute alcohol withdrawal and Medically assisted alcohol withdrawal.

1.2 BACKGROUND

Alcohol is the most widely used psychotropic drug in the industrialised world; it has been used for thousands of years as a social lubricant and anxiolytic. In the UK, it is estimated that 24% of adult men and 13% of adult women drink in a hazardous or harmful way[3]. Levels of hazardous and harmful drinking are lowest in the central and eastern regions of England (21–24% of men and 10–14% of women). They are highest in the north (26–28% of men, 16–18% of women)[3]. Hazardous and harmful drinking are commonly encountered amongst hospital attendees; 12% of emergency department attendances are directly related to alcohol[4] whilst 20% of patients admitted to hospital for illnesses unrelated to alcohol are drinking at potentially hazardous levels[5]. Continued hazardous and harmful drinking can result in dependence and tolerance with the consequence that an abrupt reduction in intake might result in development of a withdrawal syndrome. In addition, persistent drinking at hazardous and harmful levels can also result in damage to almost every organ or system of the body. Alcohol-attributable conditions include liver damage, pancreatitis and the Wernicke's encephalopathy. Key areas in the investigation and management of these conditions are covered in this guideline.

Many other and diverse conditions are associated with chronic alcohol misuse, which will not be covered in the guideline. There are examples listed in Table 1-1 below.

Table 1-1. Conditions associated with chronic alcohol misuse.

Acute	Chronic
Accidents and injury	Accidents and injury
Acute alcohol poisoning	Brain damage
Aspiration pneumonia	Oesophagitis
Oesophagitis	Dementia
Mallory-Weiss syndrome	Gastritis
Gastritis	Wernicke-Korsakoff syndrome
Pancreatitis	Malabsorption
Cardiac arrhythmias	Cerebellar degeneration
Cerebrovascular accidents	Malnutrition
Neuropraxia	Marchiafava-Bignami syndrome
Myopathy/rhabdomyolysis	Pancreatitis
Hypoglycaemia	Central pontine myelinolysis
	Liver damage
	Peripheral neuropathy

Fatty change
Myopathy
Hepatitis
Osteoporosis
Cirrhosis
Skin disorders
Hypertension
Malignancies
Cardiomyopathy
Sexual dysfunction
Coronary heart disease
Infertility
Cerebrovascular accidents
Fetal damage

During the writing of the guideline, the GDG has given consideration to the management of patients according to their gender, age and ethnic origin. Where evidence is age-specific, this is reflected in the recommendations. Among ethnic groups there is variability in the dose and pattern of alcohol consumption [6] and possibly also in the susceptibility to develop alcohol-related cirrhosis[7]. This evidence may have an impact on the recommended sensible limits of alcohol consumption (see public health guideline) for specific ethnic groups. In general, however, regardless of susceptibility, the management of the alcohol use disorder is largely the same across ethnic groups. Where the evidence suggests otherwise, this has been reflected in the recommendation.

1.3 METHODOLOGY

1.3.1 AIM

This piece of guidance was developed by the National Collaborating Centre for Chronic Conditions (NCC–CC) who on 1 April 2009 merged with three other UK collaborating centres to form the National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC). As the evidence for this guideline was reviewed before this merger, the developers will be referred to as the 'NCC–CC' throughout the document for ease of use and remain the same individuals post merger.

The aim of the NCC–CC was to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for the management and treatment of people with alcohol-use disorders;
- is based on best published clinical and economics evidence, alongside expert consensus;
- takes into account patient choice and informed decision-making;
- defines the major components of NHS care provision for people with alcohol-use disorders;
- details areas of uncertainty or controversy requiring further research; and
- provides a choice of guideline versions for different audiences.

1.3.2 SCOPE

The guideline was developed in accordance with a scope which detailed the remit of the guideline originating from the Department of Health and specified those aspects of care for people with alcohol-use disorders to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE[1,2]. The full scope is shown in Appendix A.

1.3.3 AUDIENCE

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with alcohol-use disorders and their carers
- patient support groups
- commissioning organisations
- service providers

1.3.4 INVOLVEMENT OF PEOPLE WITH A HISTORY OF ALCOHOL-USE DISORDERS

The NCC–CC was keen to ensure that the views and preferences of people with alcohol use disorders and their carers informed all stages of the guideline. This was achieved by:

- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project.
- having a person representing the service users' and carers' needs on the GDG.
- the inclusion of patient groups as registered stakeholders for the guideline.

1.3.5 GUIDELINE LIMITATIONS

- NICE clinical guidelines usually do not cover issues of **service** delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature reviews of all pharmacological toxicity or effects of an intervention. NICE expect the guidelines to be read alongside the Summaries of Product Characteristics.

1.3.6 OTHER WORK RELEVANT TO THE GUIDELINE

► **Related NICE clinical guidelines**

- Interventions in schools to prevent and reduce alcohol use among children and young people. NICE public health guidance 7 (2007). Available from www.nice.org.uk/PH007
- Community-based interventions to reduce substance misuse among vulnerable and disadvantaged children and young people. NICE public health guidance 4 (2007). Available from www.nice.org.uk/PHI004
- Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE clinical guideline 32 (2006). Available from; www.nice.org.uk/CG032

►**In development**

- School, college and community-based personal, social and health education focusing on sex and relationships and alcohol education. NICE public health guidance (publication expected September 2009).

- Alcohol use disorders: preventing the development of hazardous and harmful drinking. NICE public health guidance (publication expected March 2010).

- Alcohol use disorders: diagnosis and clinical management of harmful drinking and alcohol dependence. NICE clinical guideline (publication date to be confirmed).

1.3.7 BACKGROUND

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual[1,2] (see www.nice.org.uk)

The developers' role and remit is summarised in Table 1-2.

Table 1-2. Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC–CC)	The NCC–CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC–CC undertakes commissions received from the National Institute for Health and Clinical Excellence (NICE). A multiprofessional Partners' Board inclusive of patient groups and NHS management governs the NCC–CC. The NCC–CC merged with three other UK collaborating centres on 1 April 2009 to become the National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC-AC).
Technical Team	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised a GDG Chair, GDG Clinical Advisor, Health Economist, Information Scientist, Project Manager, and Research Fellows.
Guideline Development Group (GDG)	The GDG met monthly (June 2008 to July 2009) and comprised a multi disciplinary team of health professionals and people with alcohol-use disorders, who were supported by the technical team. The GDG membership details including carer and service user representation are detailed at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope. Prior to 1 April 2009 the PE comprised the NCC–CC Director, NCC–CC Assistant Director (operations), NCC–CC Assistant Director (implementation), NICE Commissioning Manager, and the NCC–CC Technical Team. Post 1 April 2009 the PE comprised the NCGC Clinical Director, NCGC Operations Director, NICE Commissioning Manager and the NCGC Technical Team.
Formal consensus	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE technical manual[1,2] .

1.3.8 THE PROCESS OF GUIDELINE DEVELOPMENT

The basic steps in the process of producing a guideline are:

- Developing clinical questions
- Systematically searching for the evidence
- Critically appraising the evidence
- Incorporating health economics evidence
- Developing health economic models
- Distilling and synthesising the evidence and writing recommendations
- Grading the evidence statements
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline.

► Developing evidence based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and PE refined and approved these questions, which are shown in A.3.

► Searching for and identifying the relevant evidence

The Information Scientist developed a search strategy for each question. Key words for the search were identified by the GDG.

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the clinical questions. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters. Non-English language studies were not reviewed and were therefore excluded from searches.

Each database was searched up to 22 June, 2009. One initial search was performed for the whole guideline topic which looked for systematic reviews, guidelines and economic papers in the relevant populations.

The clinical questions were formulated using the PICO (Population, Intervention, Comparison, and Outcome) format and this was used as a basis for constructing a search strategy. Quality assurance of search strategies were approached by checking relevant key papers were retrieved, and amending search strategies if appropriate. The questions, the study types applied, the databases searched and the years covered can be found in A.3.

When looking for health economic evidence, the search was undertaken with no date restrictions on the NHS economic evaluation database (EED), the health technology assessment (HTA) databases, and on Medline and Embase using a specific economic filter. Additionally, ad hoc searches were carried out for individual questions as required.

Titles and abstracts of retrieved papers were reviewed by the Research Fellow and Health Economist and full papers were ordered for studies potentially relevant to each

clinical question. The full papers were reviewed against pre-specified inclusion and exclusion criteria.

Review papers were checked for additional relevant studies which were then ordered. Additional papers identified by the GDG were ordered and reviewed. For areas where no RCTs, were identified other evidence (observational studies, diagnostic studies) was included (for example Wernicke's encephalopathy, diagnosis of chronic pancreatitis and referral for liver transplantation). The lack of evidence available in certain areas led to the inclusion of lower quality evidence. Study limitations included small sample sizes, with trials often underpowered for the outcomes of interest; selective reporting of outcomes and statistics; and imprecision (wide confidence intervals).

For the areas covering alcohol-related liver disease and alcohol- related pancreatitis the clinical evidence inclusion criteria covered populations of varying aetiologies (as long as alcohol was included within this). Evidence was used from both unplanned and planned admission settings for the questions relating to medically assisted withdrawal.

Full economic evaluations (cost–effectiveness, cost-utility and cost-benefit analyses), cost-consequence analyses and comparative costing studies that addressed the clinical question were included.

Studies that only reported cost per hospital (not per patient), or only report average cost–effectiveness without disaggregated costs and effects were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded. A judgement was made on a question by question basis regarding whether to include studies with a quality rating of 'very serious limitations', although these would usually be excluded.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG.

► *Appraising the evidence*

The Research Fellow or Health Economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the 'Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers' Manual [1,2]l
- NCC–CC Quality assurance document and systematic review chart.

► Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available on-line at (to be completed upon publication)

► Grading the evidence statements

See Table 1-3 for the levels of evidence for interventional studies and Table 1-4 for the levels of evidence for diagnostic studies[2].

Table 1-3. Levels of evidence for intervention [1]

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence '–' should not be used as a basis for making a recommendation (see section 7.4 of guideline development manual [1]	

Table 1-4. Levels of evidence for diagnostic studies[2]

Level of evidence	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c] Systematic reviews of level-2 studies
III	Level-3 studies[d] Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies:

- that use a blind comparison of the test with a validated reference standard (gold standard)
- in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have **only one** of the following:

- narrow population (the sample does not reflect the population to whom the test would apply)
- a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- a comparison between the test and reference standard that is not blind
- case-control design

[d] Level-3 studies are studies that have at least two or three of the features listed for level-2 studies.

► Assessing cost–effectiveness of interventions

It is important to investigate whether healthcare interventions are cost–effective as well as clinically effective. That is they offer good value for money. This helps us to get the most health gain from available NHS resources. In any healthcare system resources are finite and choices must be made about how best to spend limited budgets. We want to prioritise interventions that provide a high health gain relative to their cost.

Cost–effective analysis compares the costs and health outcomes of two or more alternative healthcare interventions. The criteria applied to an intervention to be considered Cost–effective were either:

a) The intervention dominated other relevant strategies – that is, it is both less costly in terms of resource use and more clinically effective when compared to other relevant strategies
b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compare with the next best strategy

Where health outcomes were not expressed in QALYs or economic evidence was not available the GDG made a judgement based on the available evidence.

The GDG agreed two priority areas for original health economic modelling for the guideline. The first analysis undertaken assessed the in-hospital management of patients with acute alcohol withdrawal. The second compared surgical and endoscopic procedures for treating patients with chronic pancreatitis. See A.4 and A.5 for full reports. A summary of relevant results is also included in each relevant chapter of the guideline.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the models.
- Models were based on clinical evidence identified from the systematic review of clinical evidence.
- Model inputs and assumptions were reported fully and transparently.
- Sensitivity analyses were undertaken to explore uncertainties in model inputs and methods.
- Costs were estimated from an NHS perspective.

► Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence-base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations .

The GDG also reached agreement on the following:

- recommendations as key priorities for implementation
- key research recommendations
- algorithms .

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation in practice
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced for NICE following publication in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

► Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- *Clinical introduction:* sets a succinct background and describes the current clinical context

- *Clinical methodological introduction:* describes any issues or limitations that were apparent when reading the evidence base. Point estimates (PE) and confidence intervals (CI) are provided for all outcomes in the evidence tables available at (to be completed upon publication). In addition within the guideline PE and CI are cited in summary tables for the evidence that pertains to the key priorities for implementation. In the absence of a summary table PE and CI are provided in the narrative text when the outcome adds something to the text and to make a particular point. These may be primary or secondary outcomes that were of particular importance to the GDG when discussing the recommendations. The rationale for not citing ***all*** statistical outcomes is to try to provide a 'user friendly' readable guideline balanced with statistical evidence where this is thought to be of interest to the reader.

- *Clinical evidence statements:* provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest. Where the evidence statements are considerable the GDG have attempted to summarise these into a useful summary.

- *Health economic methodological introduction:* as for the clinical methodological introduction, describes any issues or limitations that were apparent when reading the evidence base.

- *Health economic evidence statements:* presents, where appropriate, an overview of the cost effectiveness / cost comparison evidence-base, or any economic modelling.

- *From evidence to recommendations:* this section sets out the GDG's decision-making rationale and aims to provide a clear and explicit audit trail from the evidence to the evolution of the recommendations.

- *Recommendations:* provides stand alone, action orientated recommendations.

- *Evidence tables:* The evidence tables are not published as part of the full guideline but are available on-line at (to be completed upon publication). These describe comprehensive details of the primary evidence that was considered during the writing of each section.

► *Writing the guideline*

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

Table 1-5. Versions of the guideline

Full version:	Details the recommendations, the supporting evidence base and the expert considerations of the GDG and available online at (complete upon publication)
NICE version:	Documents the recommendations without any supporting evidence. Available at (to be completed upon publication)
'Quick reference guide':	An abridged version. Available online upon publication
'Understanding NICE guidance':	A lay version of the guideline recommendations Available online upon publication

► ***Updating the guideline***

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published up until 22 June 2009 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Following publication and in accordance with the technical manual, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The Nation Collaborating Centre for Chronic Conditions (now a part of the National Clinical Guideline Centre for Acute and Chronic Conditions) disclaim any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

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2 ACUTE ALCOHOL WITHDRAWAL

2.1 INDICATIONS FOR ADMISSION TO HOSPITAL CARE

2.1.1 CLINICAL INTRODUCTION

Approximately 40% of individuals who misuse alcohol will develop an acute alcohol withdrawal syndrome when they abruptly stop or substantially reduce their alcohol consumption. Most patients manifest a 'minor symptom complex or syndrome', which may start as early as six to eight hours after an abrupt reduction in alcohol intake. It may include any combination of generalized hyperactivity, anxiety, tremor, sweating, nausea, retching, tachycardia, hypertension and mild pyrexia. These symptoms usually peak between 10 to 30 hours and subside by 40 to 50 hours. Fits may occur in the first 12 to 48 hours and only rarely after this. Auditory and visual hallucinations may develop; these are characteristically frightening and may last for five to six days.

Delirium tremens (DTs) occurs uncommonly, perhaps in less than 5% of individuals withdrawing from alcohol. The syndrome usually starts some 48 to 72 hours after cessation of drinking and is characterized by coarse tremor, agitation, fever, tachycardia, profound confusion, delusions and hallucinations. Convulsions may herald the onset of the syndrome but are not part of the symptom complex. Hyperpyrexia, ketoacidosis, and profound circulatory collapse may develop.

Minor degrees of alcohol withdrawal are commonly encountered and individuals can be managed without recourse to specific therapy. However, patients with moderate or severe alcohol withdrawal symptoms should be sedated to prevent exhaustion and injury.

Evidence of physical dependency should always be sought because of the management implications; early morning retching, tremor, anxiety and irritability, ingestion of alcohol before midday, amnesia and "blackouts" are all suggestive. A history of previous withdrawal fits and the development of DTs clearly indicate dependence. Guidance regarding screening for dependence will be included in ‘Alcohol use disorders: diagnosis and clinical management of harmful drinking and alcohol dependence’ (NICE clinical guideline in development). Individuals who are known or are suspected of being dependent on alcohol may require help to withdraw from alcohol.

For the purposes of this guideline, medically-assisted withdrawal from alcohol with be referred to as (i) planned, which as the name implies is an elective process which is usually undertaken in the community or else as part of a planned programme within

addiction services; or (ii) unplanned which occurs when patients stop or suddenly reduce their alcohol intake either inadvertently because of an intercurrent illness, because they make a conscious decision to stop or were inadvertently deprived of alcohol, for example, following an accident. These patients may present to their GP or to acute hospital services.

Making the decision about whether a person presenting with alcohol withdrawal needs admission to hospital is impacted by the severity of the syndrome, the person's co-morbidities and the reason for the presentation. If the reason for presentation is an intercurrent illness that of itself requires admission, then the decision is made and the management of the withdrawal will occur in tandem. Very often however, the withdrawal symptoms are not life threatening and are the sole reason for presentation and there exists variation in admission practices for this cohort across the United Kingdom.

There is no doubt that some patients who wish to stop drinking but who have difficulty accessing the required services will deliberately stop drinking in order to gain admission to hospital to complete the process.

The decision whether patients with acute alcohol withdrawal need admission depends on a variety of factors. The first consideration would be the effectiveness of a hospital admission for medically-assisted withdrawal from alcohol; not only in managing the acute condition, but also in terms of facilitating long term abstinence. This will, in turn, depend on the local availability of, or liaison with, follow-up services aimed at relapse prevention. The second would be the risks involved with discharging the patient with a view to subsequent admission for elective withdrawal versus an immediate admission to complete the withdrawal process. This is of particular importance if it could be shown that elective or planned alcohol withdrawal is more effective. Given that many of these patients will undergo more than one medically-assisted withdrawal from alcohol, the risk of repeating this process is critical. One such proposed risk is the 'kindling effect'; where the severity of the withdrawal symptoms increases after repeated withdrawal episodes. If this were shown to be the case, then the number of medically-assisted withdrawal episodes should perhaps be limited. Weighed up against these concerns is the sincere wish to do the best for an individual who wishes to stop drinking and the need to prevent them from developing severe withdrawal symptoms.

Therefore, the clinical questions asked, and upon which a literature search was undertaken, were:

'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?'

2.1.2 Clinical Methodological Introduction

No studies were identified that looked at the benefits and harms of unplanned medically-assisted withdrawal compared with planned medically-assisted withdrawal. With respect to the question of whether unplanned medically-assisted withdrawal is 'safe', studies were included that looked at the association between the number of previous medically-assisted withdrawals and the incidence of seizures, risk of developing DTs or severity of withdrawal. Because there were a large number of potentially confounding variables, only studies that applied multivariate, covariate, regression or discriminant function analyses were included. Nine studies were excluded because they reported the results of univariate analysis only. Studies with a sample size of 50 or fewer were excluded from the evidence review.

For the question of what criteria should be used to admit a patient with acute alcohol withdrawal for unplanned 'emergency' withdrawal from alcohol, studies were included if they looked at factors that were potential predictors of severe withdrawal, seizure incidence or the development of DT, namely: age, history of a seizure, history of DTs, history of severe withdrawal, previous drinking history and breath or blood alcohol level.

Studies were included if they reported on individuals admitted for planned or unplanned medically-assisted withdrawals, but restricted to acute, inpatient settings only. Only one study specifically stated that people were recruited through a registry of trauma patients (and therefore represent a population of patients who may require unplanned emergency medically-assisted withdrawal in the general hospital setting) [8].

Very few studies described how they operationally defined 'detoxification', for example whether they included medically-assisted withdrawals only. One important methodological limitation is the retrospective nature of the data collection regarding the number of previous episodes of medically assisted withdrawals. Also the majority of studies obtained this information from hospital notes and thus the information may be of questionable accuracy. The table below summarises the methodological characteristics of the studies included in parts (a) and (b) of the question.

In one study the effect of multiple withdrawal episodes on cognitive function was assesses using a task of frontal lobe function (the Stroop task), a maze learning and vigilance task[9]. Cognition was compared in individuals who had undergone two or fewer medically-supervised detoxifications (LO, N=36) with those who had undergone two or more (HIGH, N=6) and a control group of 'mild to moderate' drinkers (CON, N=43). The patients were undergoing inpatient treatment and had been off treatment for alcohol withdrawal for at least two weeks prior to testing.

See Table 2-1for a summary of study characteristics.

Table 2-1. Summary of the study design, patient population, incidence of previous detoxifications and incidence of withdrawal problems, seizures and DTs.

Study	Patient population	Mean no. of previous detoxifications (range)	Incidence of withdrawal problems	Incidence of seizures	Incidence of DT
MALCOLM 2000 [10] Prospective cohort 2++	N=136 Patients with alcohol dependence and withdrawal (DSM-IV) Inclusion: ≥ 26 Mini mental state examination CIWA-Ar ≥ 10 Male and female	Comparison between 0 to 1 and multiple detoxifications (range 2 to 5)	NR	NR	NR
SCHUCKIT 1995[11] Prospective cohort 2++	N=1648 Patients who were alcohol dependent	Previous total no. of withdrawal episodes: History of	NR	NR	188/1648 (11%) patients experienced delirium

Study	Patient population	Mean no. of previous detoxifications (range)	Incidence of withdrawal problems	Incidence of seizures	Incidence of DT
	Setting: Not specified Male and female	seizure/DT 28 (SD 34) versus no history 16 (27)			tremens,
WETTERLING 2001[12] Prospective cohort 2++	N=723 Males and females admitted to a ward in a general hospital specialising in detoxification	Mean number of prior inpatient detoxifications 3 (SD 6.5)	100/723 (14%) severe withdrawal syndrome (measured on Alcohol Withdrawal Syndrome scale [13])	Not reported	61/723 (8%)
BOOTH AND BLOW 1993[14] Retrospective cohort 2+	N=6818 Male patients admitted for short inpatient detoxification. Primary diagnosis of alcohol dependence	Previous number of alcohol specific hospitalisation (previous 3 years): Withdrawal problems mean 0.95 (SE 0.10) versus no withdrawal problems 0.82 (0.03)	461/6818 (7%) withdrawal problems (DT, alcoholic hallucinations and alcoholic dementia) in index hospitalisation.	Unspecified seizures 193/6818 (3%)	NR
LUKAN 2002[8] 2+	N=1856 Patients admitted for trauma who developed DT whilst in hospital or presenting with a positive blood alcohol concentration (BAC) on admission. Setting: General hospital	NR	NR	NR	105/1856 (6%)
KRAEMER 1997[15] Retrospective case series 3	N=284 Patients with alcohol withdrawal	No. of prior alcohol treatment programs: mean 1	NR	Current seizure (index hospitalisation) 0%	Current DT (index hospitalization) was 3/284 (1%)

Study	Patient population	Mean no. of previous detoxifications (range)	Incidence of withdrawal problems	Incidence of seizures	Incidence of DT
	Setting: alcohol detoxification unit Almost exclusively male population	(range 0 to 3)		Past withdrawal seizures ranged from 1/21 (5%) (≥ 70 years) to 17/74 (23%) (50 to 59 years)	past DT ranged from 3/21 (14.3%) (≥ 70 years) to 28/74 38% (50 to 59 years)
LECHTENBERG 1991[16] Retrospective case series 3	N=400 Patients requesting admission for alcohol detoxification Setting: Alcoholism service Patient population: males and females	Mean number of admissions for detoxification 2.1 (SD 2.7)		84/400 (21%) of patients had a history of a seizure. No seizures were reported in the current hospital admission for detoxification.	
LECHTENBERG 1992[17] Retrospective case series 3	N=500 Patients with alcoholism who were at potential risk of: Dangerous or disabling withdrawal, high risks of seizures, DT or hallucinations, failure of previous outpatient detoxification, unstable social situation (admission criteria) Setting: Alcohol detoxification unit Male and female	Mean number of admissions for detoxification 2.1 (SD 2.6)		There were no seizures during the current episode of withdrawal 55/98 (56%) patients reported a history of alcohol withdrawal seizures	

Study	Patient population	Mean no. of previous detoxifications (range)	Incidence of withdrawal problems	Incidence of seizures	Incidence of DT
PALMSTIERNA[18] Prospective case series 3	N=334 Patients seeking treatment for alcohol withdrawal Setting: Psychiatric and dependency emergency unit Patient population: male : female	NR	43% history of DT	139/334 (42%) had a previous epileptic seizure 23/334 (7%) had a epileptic seizure in the past 48 hours	145/334 (43%) had previously experienced alcohol withdrawal delirium
FERGUSON 1996[19] Retrospective cohort 2++	N=200 Patients with alcohol withdrawal or detoxification Setting: Internal medicine hospital at general hospital Male and female	Proportion of patients who had undergone a previous withdrawal Mean 52%	NR	NR	48/200 (24%) developed delirium tremens
KRAEMER 2003[20] Retrospective case series 3	N=284 Patients admitted to an acute inpatients detoxification unit Setting: Inpatient detoxification unit	NR	The incidence of severe withdrawal was 25% .	NR	NR

NR – not reported

2.1.3 CLINICAL EVIDENCE STATEMENTS

►Previous detoxifications and severity of alcohol withdrawal

The following measures of severity of withdrawal were significantly associated with the number of previous detoxifications or were reported to be significantly different between patients with no or a small number of previous detoxifications and those with a high number:

- A slower rate of decline on the CIWA-Ar day 0 to 4 of withdrawal associated with multiple detoxifications (multiple versus 0 to 1 detoxifications; $p<0.05$).[21]
  Level 2++

- Severe withdrawal (requirement for 600 mg or more, total, cumulative benzodiazepine (expressed in chlordiazepoxide equivalents) was significantly associated with participation in two or more prior alcohol treatment programs (OR 2.6 [95%CI 1.3 to 5.6]; p=0.01).[20]
  Level 3

The following measures of severity of withdrawal were not significantly associated with the number of previous detoxifications or were not significantly different between patients with a low and those with a high number of detoxifications:

- The CIWA-Ar score on admission was not significantly related to the number of previous admissions (not significant).[21]
  Level 2++

- The severity of alcohol withdrawal (alcohol withdrawal syndrome scale) was not significantly related to the number of previous detoxifications (not significant).[12]
  Level 2++

- The frequency of alcohol-specific hospitalisations was not significantly associated with withdrawal problems (DT, alcoholic hallucinations and alcoholic dementia during hospitalisation) (withdrawal problems versus no withdrawal problems mean 0.95 (SE0.10) versus 0.82 [0.03] not significant).[14]
  Level 2+

►***Previous detoxifications and incidence of seizures***

Four studies report that patients with a history of previous detoxifications or withdrawals were significantly more likely to experience a seizure:

- There was a significant difference between those patients who had unspecified seizures in the index hospitalisation and those who did not and the mean number of previous alcohol-specific hospitalizations (with a primary diagnoses of alcohol dependence and acute alcohol intoxification) (in the previous 3 years) (mean 1.48 [SE0.23] versus 0.81 [SE0.03]; MD 0.67; p<0.01). [14]
  Level 2+

- Two studies reported a significant association between the history of a seizure and the total number of previous detoxification admissions (mean 2, R^2-Ad 0.035, F=13.2; p<0.001) [16](mean 2, R^2-Ad 0.041, F=15.1; p<0.0001) [17].
  Level 3

- A history of DTs and/or convulsions compared with no history of DTs and/or convulsions was significantly associated with a history of more withdrawal episodes (28 versus 16) (OR 1.01, 95%CI 1.00 to 1.02; p<0.01) [11].
  Level 2++

►***Previous detoxifications and incidence of DTs***

One study reported no significant association between previous detoxification history and the development of DTs (0.94; 95%CI 0.68 to 1.29;p=0.70) [19].

Level 2++

►***Cognitive impairments***

There were no significant differences (ANCOVA) reported between patients with a high number of previous detoxifications and those with a low number on the Stroop task (errors 2.67 [SE1.73] versus 2.62 [0.55]; MD 0.05; ns, maze learning [errors 1.73 {SE0.34} versus 1.47 {0.41}]; MD 0.26; not significant) or vigilance tasks (number correct 0.67 (SE0.07 versus 0.79 [0.02]; MD 0.12; ns)[9].

Level 2++

Factors associated with the incidence of seizures

►***Previous history of a seizure***

No studies reported on this outcome.

►***Previous history of DT***

No studies reported on this outcome.

► ***Age***

Two studies reported that:

- The prevalence of seizure history was not significantly correlated with age (not significant). [16],[17]

  Level 3

► ***Alcohol consumption/history***

The following were not correlated with prevalence of seizure history:

- Years of alcoholism [16]; R2-AD 0.007; F=20.3; p=0.1064)[17].

  Level 3

- A history of DTs and/or convulsions compared with no history of DTs and/or convulsions was significantly associated with the higher number of drinks in 24 hour (lifetime) (41 versus 25) (OR 1.02, 95%CI 1.01 to 1.03; p<0.001) [11].

  Level 2++

► ***Alcohol level on admission***

No studies reported on this variable in relationship to the incidence of seizures.

► *Factors associated with the risk of developing DT*

One study developed a model for identifying patients with a high risk of developing delirium tremens after assessment in the emergency department. Five risk factors were significantly associated with its occurrence, (of relevance to those factors included in this evidence review):

- a history of previous withdrawal seizures (R^2=0.068, t=2.35; p=0.019). A previous history of withdrawal seizures independently contributed 6.8% to the risk of developing DTs [18].

  Level 3

- a history of previous episodes of DTs (R^2=060, t=2.07; p=0.039). A previous history of alcohol–related DTs contributed 6% to the risk of developing DTs [18].

  Level 3

- Signs of overactivity of the autonomic nervous system accompanied by an alcohol concentration of more than 1 gram per litre of body fluid (R^2=0.129 t=3.11; p=0.002) [18].
  Level 3

- alcohol concentration of more than 1 gram per litre of body fluid not accompanied by signs of autonomic hyperactivity was not associated with the risk of developing DTs (ns in univariate analysis and therefore not entered into the regression model) [18]
  Level 3

►***Age***

One study on trauma patients reported that:

- age > 40 years was a significant predictor of DTs (OR adjusted 2.98; 95%CI 1.97 to 4.51; p<0.001) [8].
  Level 2+

►***Alcohol consumption/history***

One study reported that:

- more days since the last drink was an independent predictor of the development of DTs (OR 1.3; 95%CI 1.09 to 1.61; p=0.0047) [19].
  Level 2+

►***Alcohol level on admission***

One study reported that:

- blood alcohol concentration ≥ 43 mmol/L (200 mg/dL) was a significant predictor of the development of DTs (DT present versus DT absent 52/104 [60%] versus 833/1751 [48%]; OR 1.69 [95%CI 1.08 to 2.62]; p=0.02)[8].
  Level 2++

Factors associated with severe alcohol withdrawal

►***Previous history of a seizure***

One study reported that:

- a history of withdrawal seizures was not a significant predictor of severe withdrawal (symptom-triggered regimen, 600 mg or more, total, cumulative benzodiazepine [expressed in chlordiazepoxide equivalents]) [20].
  Level 3

► ***Previous history of DT***

One study reported that:

- a history of DTs was a significant predictors of severe withdrawal (600 mg or more, total, cumulative benzodiazepine (expressed in chlordiazepoxide equivalents) (OR 2.9; 95%CI 1.3 to 6.2; p=0.007) [20].
  Level 3

► ***Age***

Two studies reported no significant associations between age:

- maximum Alcohol Withdrawal Scale (AWS) score (not significant) [12].
  Level 2++

- maximal CIWA-Ar score (not significant) [22].
  Level 3

- Initial CIWA-Ar score (not significant) [22].
  Level 3

► ***Alcohol consumption/history***

Two studies reported no significant associations between drinking consumption and drinking history and:

- Withdrawal severity (maximum AWS score) and alcohol duration, alcohol intake/drinking day (not significant) [12].
  Level 2++

There was no significant association between severity of withdrawal (600 mg or more, total, cumulative benzodiazepine [expressed in chlordiazepoxide equivalents]) and:

- daily alcohol intake (not significant) [20]
- number of drinking days over past month (not significant) [20].
  Level 3

► ***Alcohol level on admission***

One study reported on the association between breath alcohol level on admission and the severity of withdrawal. The results were reported separately for admission to a non-medical setting and a medical setting [23].

Level 2+

- **Non-medical setting**

  Linear regression analysis showed a significant relationship between breath alcohol levels on admission and severity of withdrawal (amount of chlordiazepoxide used in first 48 hours) (R^2=0.26;p<0.0001). When patients were classified in to two groups based on the median level of breath alcohol on admission (≤ 33 mmol/L [150 mg/dL versus > 33 mmol/L]) higher levels were associated with more severe adverse outcomes, including transfer to acute care hospital for medical detoxification and a maximum withdrawal assessment score of greater than 6 (indicating medical consultation is required). When the same threshold was applied to the medical setting, the threshold distinguished between those patients who required a total of 50 mg chlordiazepoxide or less and those who required more [23].

  Level 2+

- **Medical setting**

  Linear regression analysis showed a significant relationship between breath alcohol levels on admission and severity of withdrawal (R^2=0.41; p<0.0001)[23].

  Level 2+

2.1.4 Health Economic methodological Introduction

One UK cost-effectiveness analysis was identified and was presented to the GDG.

Parrot 2006 [24] presented a cost-utility analysis (reporting cost per QALY gained) based on a case series (n = 54) from a direct-access alcohol detoxification service in Manchester (Smithfield Centre). This service offered a 10-day detoxification including three to four days for the management of withdrawal. The following six to seven days involved social care interventions. All non-referred admissions for alcohol detoxification from April to November 1998 were prospectively followed for a 6-month period to collect quality of life and resource use data (non-direct-access patients formally referred from other services or professionals were excluded). Retrospective resource use data were collected for the 6-month period before the admission by interview/questionnaire.

The costs incorporated in the analysis were the 10-day treatment cost at the centre, and the costs related to health services, alcohol services, criminal justice services, and social services. Patient-level quality of life data were collected on admission to the centre and 6 month later using the EuroQol (EQ-5D) questionnaire[25]. No sensitivity analysis was undertaken.

2.1.5 Health Economic Evidence Statements

Results of the Parrot 2006 study[24] were calculated comparing data from the case series pre- and post-detoxification. Two cost-effectiveness ratios were presented. The first cost-effectiveness ratio considered the QALY gain from admission to 6 months post-discharge (0.033), and the 10-days detoxification cost only. The result indicated a cost of £33,727 per QALY gained. The second cost-effectiveness ratio presented considered the same QALY difference (0.033), but estimated the impact on costs by comparing 6-month costs pre- and post-detoxification from a broader perspective including health service costs, alcohol service costs, criminal justice service costs, and social service costs. The result indicated a cost of £65,454 per QALY gained. If the costs relating to the criminal justice services are excluded, then the costs would be £69,090 per QALY gained – this would be the usual NICE reference case.

The Parrot analysis[24] was based on outcomes collected from a case series pre- and post-treatment. This method might be more biased than a cohort study comparing an intervention with a control group. However, the magnitude and direction of this bias is unknown. The small size of the case series (n=54) is another limitation of this study. Finally, results from this analysis need to be considered carefully as the study was undertaken on a specialist alcohol unit with a potentially different caseload to that of a general hospital.

2.1.6 From evidence to recommendations

The GDG recognised this is a very difficult area in which to produce guidance as each individual is different and the clinical problem is often compounded by social problems. It was emphasised that these clinical decisions must be made with compassion and with the patient's best interests in mind.

People with a co-incident medical problem requiring admission were excluded from the review as these individuals will be admitted for the co-incident problem and started on a regimen to manage their withdrawal from alcohol.

The majority of the studies collated data retrospectively which raises questions about the accuracy of reporting.

The GDG noted the evidence review did not find that repeated unplanned medically assisted withdrawals from alcohol caused harm. Some low quality studies supported an

association, but there were as many studies showing no association. While the kindling hypothesis was not disproved, the group agreed there was not enough clinical evidence in favour of the hypothesis to support a recommendation.

As there were no studies comparing the efficacy of hospital admission for an unplanned medically assisted withdrawal from alcohol with either a planned admission or planned out-patient management it was not possible to make an evidence-based recommendation regarding the efficacy of unplanned medically assisted withdrawal from alcohol. Nevertheless, consensus opinion based on experience within the group was that unplanned medically assisted withdrawal from alcohol in isolation is rarely an effective long-term treatment for alcohol dependence. It may be the case that patients who have planned to stop drinking and present to general hospitals may have good long-term outcomes with regard to abstinence if the appropriate follow up services focusing on relapse prevention are provided on discharge. At present, however, there is often a delay between discharge and the institution of relapse prevention treatment. It was felt that, on balance, these patients were likely to get better long-term benefits by undergoing a planned withdrawal in an elective manner, organised through addiction services, with the relevant and appropriate follow-up.

As such, the GDG emphasised the need to direct people presenting with withdrawal towards alcohol addiction services and encourage them to undergo planned withdrawal (to be covered in 'Alcohol use disorders: diagnosis and clinical management of harmful drinking and alcohol dependence' [NICE clinical guideline in development]). The risks of sudden withdrawal from alcohol should be made clear to the person and advice should be given about how best to engage with the most appropriate local addiction services.

The GDG agreed, by expert consensus, that individuals may also need admission due to the severity or predicted severity of the syndrome. More specifically, if a person presents following or in a withdrawal seizure or delirium tremens they should be admitted for medical care. In addition the evidence was examined to identify which factors confer a high risk of the withdrawal episode progressing to either seizure or delirium tremens. These factors have been investigated [18] and have been identified as:

- history of alcohol withdrawal seizures
- a history of DTs
- co-incident infection
- tachycardia
- signs and symptoms of autonomic over-activity with blood ethanol concentration > 1,000mg/L

The GDG considered that these factors should be used as predictors of a severe withdrawal episode and accepted as an indication that the person should be admitted for medically assisted withdrawal. While some of these features may not mandate admission if the current withdrawal episode is mild, it was agreed they each have predictive utility in a clinical setting.

All of the studies reviewed were in adult populations although age was not restricted when undertaking the literature search. As such, the GDG agreed that while the presentation of a young person with alcohol withdrawal is rare it is associated with a unique set of problems and management should always include addressing any underlying long-term psychosocial issues. The GDG agreed that this population is particularly vulnerable and that admission should be considered at a lower threshold in those under 18 and advised in those under 16. The GDG recognises that intoxication is a more common problem than withdrawal in this age group.

No correlation was found between age and the severity of withdrawal: however, it was noted that frail people may be more susceptible to post-discharge injury from falls, slips and the like. The GDG agreed there should be a lower threshold for admission for the medical management of alcohol withdrawal in this population. They recognised that biological is more important than chronological age.

The GDG noted that a person's level of social support outside the hospital setting can make a considerable difference to the outcome and may impact upon the decision as to whether they will require admission or not.

2.1.7 Recommendations

R1 Offer admission to hospital for medically assisted withdrawal from alcohol, people with, or who are assessed to be at high risk of developing, alcohol withdrawal seizures or delirium tremens.

R2 For people who are alcohol dependent but not admitted to hospital, offer advice to avoid a sudden reduction in alcohol intake and information on how to access appropriate support services.

R3 Consider a lower threshold for admitting certain vulnerable people for unplanned medically assisted withdrawal (for example, people who are frail, have cognitive impairment or multiple comorbidities, lack social support, have learning difficulties, or are aged 16 or 17 years).

R4 Admit to hospital for physical and psychosocial assessment, young people under the age of 16 years with acute alcohol withdrawal.

2.1.8 Research Recommendations

RR1. What is the clinical and cost effectiveness of admitting patients attending hospital in mild or moderate acute alcohol withdrawal for medically assisted withdrawal and follow-up compared with no admission and follow-up for abstinence?

2.2 TREATMENT FOR WITHDRAWAL

2.2.1 CLINICAL INTRODUCTION

Several classes of drug can be used to treat the symptoms of alcohol withdrawal. The most widely used are the benzodiazepines, but within this class there are many drugs, each with a different bioavailability and half life. In addition, other agents such as anticonvulsants and antipsychotics have been used.

During a planned medically-assisted withdrawal (to be covered in 'Alcohol use disorders: diagnosis and clinical management of harmful drinking and alcohol dependence' [NICE clinical guideline in development]), the aim is to prevent symptoms of withdrawal. In the acute, unplanned setting patients may present with withdrawal of varying severity which may include seizures or delirium.

The goals of treatment when managing withdrawal are to minimize the symptoms, promote the comfort and dignity of the patient and prevent complications such as seizures and delirium tremens. Care must be taken not to over-sedate the patient, and certain groups are more susceptible to complications than others; most notably those with respiratory illness or liver failure.

In current UK practice, benzodiazepines are the most commonly used agents, with chlordiazepoxide and diazepam favoured in many places. Others favour clomethiazole or carbamazepine.

The clinical question asked, and upon which the literature search was undertaken, was:

> *'What is the safety and efficacy of a benzodiazepine (chlordiazepoxide or diazepam, alprazolam, oxazepam, clobazam, lorazepam) versus a) placebo b) other benzodiazepines benzodiazepine (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?'*

2.2.2 CLINICAL METHODOLOGICAL INTRODUCTION

For this question, studies were restricted to systematic reviews/ meta-analysis of RCTs or individual RCTs. One Cochrane systematic review on benzodiazepines for alcohol withdrawal was identified and appraised[26]. This reported on the efficacy and safety of benzodiazepines in comparison with placebo or other pharmacological intervention or other benzodiazepines.

Level 1++

The Cochrane systematic review included studies on patients who were not in acute alcohol withdrawal. In addition, some studies were on pharmacological interventions that were not relevant for the clinical question under consideration here. In addition, the

drug clomethiazole was classified as an anticonvulsant in the Cochrane and re-classified as a hypnotic (other agents) for the meta-analysis presented. After these studies had been removed, 21 out of the 56 studies were included in the meta-analysis. However, not all studies reported on the outcomes reported here. The follow-up period ranged from eight hours to 14 days.

The outcome 'therapeutic success' included measures of severity of withdrawal syndrome (for example, the CIWA-Ar score).

There was a large degree of heterogeneity in the trials with respect to sample size, patient population (for example including severity of alcohol withdrawal, inclusion/exclusion criteria) and dosage and scheduling of pharmacological agents.

No relevant papers were identified for any of the drug comparisons that reported on safety and efficacy for specific patient populations, for example older adults or adolescents.

2.2.3 Clinical Evidence Statements

See Table 2-2 for a summary of results.

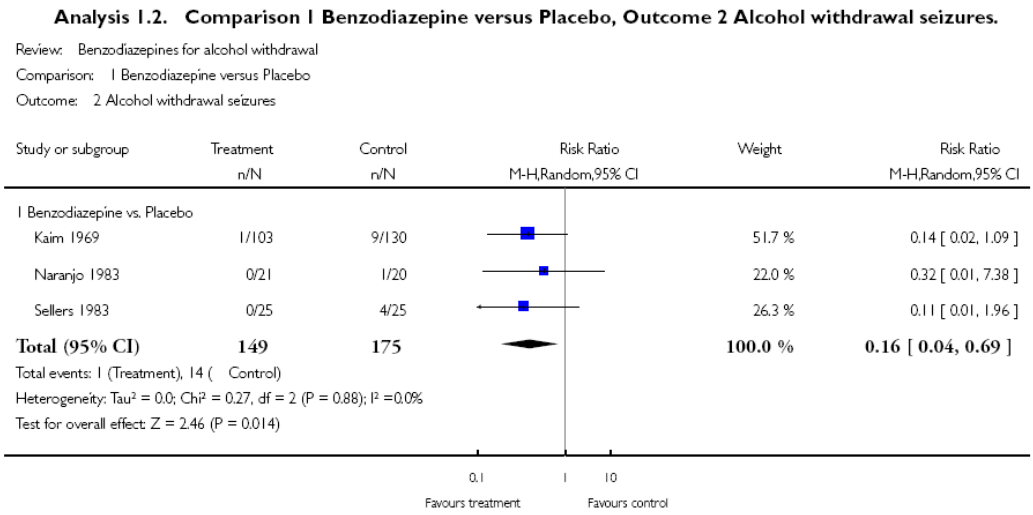
►Benzodiazepines versus placebo

Alcohol withdrawal seizures

A meta-analysis of three studies (Chlordiazepoxide N=2, Lorazepam N=1) found that benzodiazepines were significantly more effective than placebo (RR: 0.16 [95% CI: 0.04 to 0.69] p=0.01). See Figure 2-1 for the forest plot extracted from the Cochrane systematic review [26].

Level 1++

Figure 2-1. Forest plot extracted from Cochrane review[26].



1 **Table 2-2. Summary of results.**

Outcome	Benzodiazepines versus placebo	Benzodiazepines versus Benzodiazepines	Benzodiazepines versus anticonvulsant
Therapeutic success	**Chlorodiazepoxide (2 of 8 studies)** **Lorazepam** RR: 1.40 (95%CI: 0.87-2.27) p=0.2 (3 of 8 studies)	**Lorazepam versus diazepam** RR:0.95 (95% CI: 0.86 to 1.05) p=0.3 **Chlordiazepoxide versus diazepam** RR:1.17 (95% CI: 0.86 to 1.58) p=0.3 **Alprazolam versus diazepam** RR: 1 (95% CI: 0.87 to 1.13) p=0.9 **Alprazolam versus chlordiazepoxide** RR: 0.98 (95% CI: 0.88 to 1.09) p=0.7 (4 of 12 studies)	n/a
Alcohol withdrawal seizures	RR: 0.16 (95% CI: 0.04 to 0.69) p=0.01 (3 of 8 studies)	**Lorazepam versus Chlordiazepoxide** RR:5 (95% CI: 0.25 to 99.16) p=0.3 **Lorazepam versus diazepam** RR:3 (95% CI: 0.13 to 69.52) p=0.5 **Alprazolam versus Chlordiazepoxide** RR: 2.25 (95% CI: 0.74 to 6.83) p=0.2 (3 of 12 studies)	**Oxazepam versus carbamazepine** RR: 3 (95%CI: 0.13 to 70.74) p=0.5 (1 of 3 studies)
Mortality	No deaths in 8 studies	No deaths in 10 studies **Alprazolam versus Chlordiazepoxide** RR: 0.33 (95% CI: 0.01 to 7.99) p=0.5 (1 study)	No deaths in 3 studies
Side effects	**Chlordiazepoxide** RR: 1.10 (95% CI: 0.08 to 15.36) p =0.9 (1 of 8 studies)	**Lorazepam versus diazepam** RR:2.56 (95% CI: 0.35 to 18.62) p=0.4 **Chlordiazepoxide versus diazepam** RR:3 (95% CI: 0.14 to 63.15) p=0.5 (4 of 12 studies)	**Oxazepam versus carbamazepine** RR: 0.75 (95%CI: 0.44 to 1.29) p=0.3 (1 of 3 studies)
Life threatening side effects	n/a	**Chlordiazepoxide versus diazepam:** none **Alprazolam versus diazepam:** none **Alprazolam versus**	n/a

Outcome	Benzodiazepines versus placebo	Benzodiazepines versus Benzodiazepines	Benzodiazepines versus anticonvulsant
		Chlordiazepoxide RR: 0.33 (95% CI: 0.01 to 7.99) p=0.5 (3 of 12 studies)	
Discontinuation due to side effects	**Chlordiazepoxide** RR: 0.36 (95% CI: 0.02 – 8.03) p=0.5 (2 of 8 studies)	**Alprazolam versus chlordiazepoxide** RR: 1 (95% CI: 0.21 to 4.72) p=1 **Lorazepam versus diazepam** RR:1.66 (95% CI: 0.21 to 12.95) p=0.6 **Chlordiazepoxide versus diazepam** RR:3 (95% CI: 0.14 to 63.15) p=0.5 **Lorazepam versus Chlordiazepoxide:** none **Alprazolam versus diazepam** RR: 0.36 (95% CI: 0.02 to 8.47) p=0.5 (8 of 12 studies)	**Oxazepam versus carbamazepine** RR: 0.14 (95%CI: 0.01 to 2.65) p=0.19 (1 of 3 studies)
Alcohol withdrawal delirium	n/a	**Lorazepam versus diazepam** RR: 5.18 (95% CI: 0.26 to 103.15) p=0.3 **Alprazolam versus Chlordiazepoxide** RR: 1 (95% CI: 0.21 to 4.72) p=1 (2 of 12 studies)	**Oxazepam versus carbamazepine** RR: 5 (95%CI: 0.25 to 99.82) p=0.29 (1 of 3 studies)
CIWA-Ar[1] score (change from baseline) at 48hours	n/a	**Chlordiazepoxide versus diazepam** RR: 4.5 (95%CI: -2.44 to 11.44) p=0.2 (1 of 12 studies)	**Oxazepam versus carbamazepine** **Oxazepam versus carbamazepine lorazepam versus carbamazepine** WMD: -0.73 (95% CI: -2.88 to1.42) p = 0.5 (3 of 3 studies)
CIWA-Ar score (change from baseline) at end of treatment	n/a	**Chlordiazepoxide versus diazepam** RR: 3.3 (95%CI: -4.19 to 10.79) p=0.4 (1 of 12 studies)	**Oxazepam versus carbamazepine** **Oxazepam versus carbamazepine Lorazepam**

Outcome	Benzodiazepines versus placebo	Benzodiazepines versus Benzodiazepines	Benzodiazepines versus anticonvulsant
			versus carbamazepine WMD: -1.04 (95% CI: -3.45 to 1.38) p = 0.4 (3 of 3 studies)

There were no significant differences between benzodiazepines and placebo for [26]:

- therapeutic success
- mortality
- side effects
- discontinuation due to side effects .

Level 1++

►Benzodiazepines versus benzodiazepines

There were non-significant differences when one benzodiazepine was compared with another benzodiazepine for [26]:

- alcohol withdrawal seizures
- therapeutic success
- mortality
- side effects
- life threatening side effects
- discontinuation due to side effects
- alcohol withdrawal delirium
- Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) score (change from baseline) at 48 hours
- CIWA-Ar score (change from baseline) at end of treatment.

Level 1++

►Benzodiazepines versus carbamazepine

There were no significant differences when benzodiazepines were compared with anticonvulsants for [26]:

- alcohol withdrawal seizures
- mortality
- side effects
- discontinuation due to side effects
- alcohol withdrawal delirium
- CIWA-Ar score (change from baseline) at 48 hours
- CIWA-Ar score (change from baseline) at end of treatment.

Level 1++

►Benzodiazepines versus clomethiazole

There were non-significant differences when benzodiazepines was compared with clomethiazole for [26]:

- alcohol withdrawal seizures
- therapeutic success
- mortality
- side effects
- life threatening side effects
- discontinuation due to side effects.

Level 1++

►Clomethiazole versus placebo

There were no results reported in the Cochrane systematic review for the outcomes specified [26].

Level 1++

►Carbamazepine versus placebo

No relevant papers were identified.

2.2.4 Health Economic Methodological Introduction

No relevant economic evidence was identified that assessed the cost-effectiveness of giving benzodiazepines, clomethiazole or other agents as a treatment for acute alcohol withdrawal. GDG members received a list of costs for the different drugs appraised by the clinical literature review, in association with the specific dosages as recommended for use in England and Wales[27,28].

2.2.5 Health economic evidence statement

The cost of medications for treating patients with acute alcohol withdrawal (AAW) is relatively low[27,28], and this treatment is given for a short period. The cost-impact related to this therapy is therefore likely to be small.

2.2.6 From evidence to recommendation

The research studies considered in this review assessed short-term outcomes for safety and efficacy of agents used for the prevention and treatment of symptoms of alcohol withdrawal including seizures. The trials did not capture any qualitative aspects of the patient experience (for example, safety, dignity and comfort) and the number of events recorded for each outcome was small. The incidence of reported side-effects of medication was low. No deaths were reported in any of the studies.

The GDG noted that the study sizes were small and heterogeneous with respect to inclusion / exclusion criteria and none included young people or older adults in their samples. Therefore, the study populations may not be representative of those

presenting to clinical practice especially as patients with a history of substance misuse or a concurrent medical or psychiatric condition were excluded.

The cost to the NHS for each of the agents was low and no information was available about how any of the agents affects length of hospital stay or other elements of resource use. The cost-effectiveness is therefore uncertain but given the low cost we suspect that these therapies would be considered cost-effective.

The evidence showed benzodiazepines to be more effective than placebo for the prevention of alcohol withdrawal seizures. No other significant differences were found within and across the agents considered (benzodiazepines, carbamazepine and clomethiazole). In particular, there was no evidence to support the widely held belief that clomethiazole is less safe than the other agents, although the GDG were concerned about use of this agent outside a closely monitored inpatient setting. The trial evidence available was not sufficient to reassure the GDG regarding the use of this agent outside these circumstances. The GDG noted that there is wide variation in the choice of agent used in clinical practice, which reflects the lack of evidence supporting a particular agent.

In older adults and people with compromised liver function, long-acting agents are known to accumulate. In the absence of clinical evidence supporting one agent over another, the GDG agreed on consensus that a shorter-acting agent (e.g. oxazepam or lorazepam) could be offered if there was evidence of encephalopathy. Patients with decompensated liver disease and alcohol withdrawal can be very challenging to manage. While not necessarily requiring management on liver units, it was felt that these patients would benefit from the input of a clinician experienced in the management of liver disease and encephalopathy as well as withdrawal.

2.2.7 Recommendations

R5 Offer a benzodiazepine, clomethiazole or carbamazepine to treat the symptoms of acute alcohol withdrawal.

R6 Offer hepatology advice to people with decompensated liver disease who are undergoing treatment for alcohol withdrawal

2.2.8 Research Recommendations

RR2 What is the efficacy and cost effectiveness of clomethiazole compared to chlordiazepoxide 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?

2.3 DOSING REGIMEN

2.3.1 CLINICAL INTRODUCTION

People with acute alcohol withdrawal will respond differently to the drugs used to treat this condition. This variability is dictated partly by the severity of the withdrawal, but also by the person's age and co-morbidities. As such, it is very important to deliver the appropriate dose of drugs at the right time to control the withdrawal and keep them comfortable, but not over-sedated.

Many centres across the UK have protocols recommending fixed dose regimen of drugs. However, this is only one of three possible treatment regimens (see Table 2-3 for an example of these) and the GDG's aim was to determine which is the safest and most effective for achieving the goals of therapy for acute alcohol withdrawal:

Fixed dose
In general, these regimen start with a standard dose, which is then reduced over the next several days. Most include an "as required" option to treat breakthrough symptoms.

Symptom-triggered
This type of regimen tailors treatment to the person's requirements as determined by the severity of their withdrawal signs and symptoms. As such 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. Pharmacotherapy is provided if the patient needs it and treatment is withheld if there are no symptoms of withdrawal.

Front-loaded
The loading dose regimen provides a large dose of long-acting pharmacotherapy at the start of the treatment regimen and then provides it on an 'as required' basis after this.

Table 2-3. Example of dosing regimens for acute alcohol withdrawal.

Treating alcohol withdrawal with chlordiazepoxide				
Dosing Regimen	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Fixed dose	50 to 100 mg four times daily	50 to 100 mg three times daily	50 to 100 mg twice daily	50 to 100 mg at bedtime
Symptom-triggered	50 to 100 mg every 4 to 6 hours as needed based on symptoms*	50 to 100 mg every 6 to 8 hours as needed	50 to 100 mg every 12 hours as needed	50 to 100 mg at bedtime as needed

Front-loaded^	100 to 200 mg every 2 to 4 hours until sedation is achieved; then 50 to 100 mg every 4 to 6 hours as needed	50 to 100 mg every 4 to 6 hours as needed	50 to 100 mg every 4 to 6 hours as needed	None

*These symptoms include pulse rate greater than 90 per minute, diastolic blood pressure greater than 90 mm Hg or signs of withdrawal.

^ Frequently, very little additional medication is necessary after initial loading.

When managing acute alcohol withdrawal it is important to correctly assess the person's symptoms since they guide the use of the 'as required' treatment in all three dosing regimen. Clinical judgement can be supported by tools that have been developed specifically for this purpose; most notably the revised clinical institute withdrawal assessment from alcohol (CIWA-Ar) tool[29]. This 10 point tool has become the one of the widely used observer-rated measures of alcohol withdrawal severity. We aimed to determine whether an alcohol withdrawal assessment tool compared to clinical judgement alone improved outcomes in managing the treatment of people with acute alcohol withdrawal.

The clinical questions asked, and upon which a literature search was undertaken were:

'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?

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?'

2.3.2 Clinical Methodological Introduction

Four studies were identified that compared symptom-triggered with fixed-dosing regimens [30,31,32,33].

Level 3

Two studies compared symptom-triggered management with routine hospital detoxification practice [34,35].

Level 3

Four studies compared front-loading with fixed-dose treatment regimens [36,37,38,39].

Level 2+

One further study was identified that compared symptom-triggered bolus therapy with a continuous infusion of flunitrazepam, clonidine and haloperidol[40].

Level 1+

Three of the studies comparing symptom-triggered with fixed-dosing were undertaken in patients admitted to specialised addiction service/dependency units [30,31,33]. One study was undertaken in patients admitted to general medical wards with alcohol dependence and a comorbid medical condition[32]. One of the studies excluded patients with a history of alcohol withdrawal seizures [31] and two studies included these patients [30,33]. Two of the studies almost exclusively include men [30,31].

Level 3

Of the two retrospective case series studies comparing symptom-triggered therapy with 'routine' hospital practice, one included patients with 'uncomplicated' alcohol withdrawal syndrome [35] and the other included patients admitted to a general medical service but excluded those presenting with seizure or admitted to ITU[34]. In one study routine hospital practice was defined as 'patients received medication as ordered by the admitting provider, usually a medical or psychiatry resident. Only the addiction unit used a standardized withdrawal assessment tool. Other services used vital sign parameters or non specific terminology such as 'alcohol withdrawal' for PRN orders in a less standardized way, with or without a scheduled medication taper'[35]. In the remaining study routine hospital practice referred to 'usual care - empiric benzodiazepine dosage usually on a tapering fixed-dose regimen or with as-needed doses at the discretion of medical staff but without a uniform pattern'[34].

Level 3

All the studies comparing front-loading with fixed-dosing regimens were undertaken in patients admitted to specialised addiction service/dependency units [36,37,39,38].

Level 2+

The study comparing symptom-triggered bolus therapy with a continuous infusion was undertaken in patients with trauma or gastrointestinal surgery who subsequently developed alcohol withdrawal syndrome in the intensive care unit (ICU).[40]

Level 1+

The studies differed with respect to patient populations, intervention, CIWA-Ar criteria for treatment/ no treatment, frequency of CIWA-Ar administration and treatment regimens. See table Table 2-4 below.

Table 2-4. Summary of included studies.

Reference	Study type, evidence level, intervention	Comparison
Symptom-triggered therapy versus fixed-dosing		
DAEPPEN 2002[30] RCT 1++	Symptom-triggered therapy N=56 Total no. treated with oxazepam: N=22/56 (39%)	Fixed-dose, N=61 Oxazepam every six hours, 4 doses of 30 mg and then 8 doses of 15 mg

Reference	Study type, evidence level, intervention	Comparison
	Placebo every six hours, 4 doses of 30 mg followed by 8 doses of 15 mg Plus As-needed medication (score-based dose): CIWA-Ar administered half an hour after each placebo dose Score: ≤ 7 - no medication 8-15 - 15 mg of oxazepam ≥ 15 - 30 mg of oxazepam	Plus As-needed medication as for symptom-triggered
SAITZ 1994[31] RCT 1++	Symptom-triggered N=51 Placebo every 6 hours for 12 doses Plus CIWA-Ar administered hourly: Score ≥8: 25 to 100 mg of chlordiazepoxide hourly (dose based on nurse 'judgement')	Fixed-dose N=50 Chlordiazepoxide every six hours for 12 doses (4 doses of 50mg followed by 8 doses of 25mg). Plus 'As-needed medication': CIWA-Ar administered hourly: Score ≥8: 25 to 100 mg chlodiazepoxide (dose based on nurse 'judgement')
WEAVER 2006[32] Quasi-randomised trial 2+	Symptom triggered N=91 CIWA-Ar at initial assessment and then every four hours If score > 30 hourly assessment until < 30 when it went to 4 hourly. Lorazepam dose (based on score): < 5 no medication 6 to 9 0.5 mg 10 to 19 1 mg 20 to 29 2 mg 30 to 39 3 mg > 40 4 mg	Fixed-dose, N=92 First 48 hours lorazepam 2 mg every four hours (total 12 doses) Tapering: 1 mg every 4 hours for six doses (24 hours), followed by 0.5 mg every 4 hours for 6 doses, then discontinued If score > 30 additional lorazepam ever hour as need until score < 30 for two consecutive assessments
LANGE-ASSCENFELDT[33] 2003 Retrospective	Symptom-triggered N=33 CIWA-Ar (modified German version)	Fixed-dose N=32 CMZ administered as soon as

Reference	Study type, evidence level, intervention	Comparison
chart analysis 3	administered at initial assessment and then: every two hours during day 0 (day of admission), and days 1 to 3 every 4 hour days 4 and 5 4 times daily on day 6 3 times daily on day 7 Twice daily days 8 and 9 Clomethiazole (CMZ) dose: Total score 0 to 4 - 0 mg 5 to 7 -192 mg 8 to 10 - 384 mg > 10 - 576 mg	patient exhibits first signs of alcohol withdrawal. CMZ dosage/schedule: Mild to moderate withdrawal symptoms: 1 capsule = 192 mg Initial dose 2 capsules (trial dose) Day 0 (first 24 hour) 9 to 12 capsules in 3 or 4 doses Days 1 and 2 6 to 8 capsules in 3 or 4 doses Days 3 and 4, 4 to 6 capsules in 2 or 3 doses Days 5 to 9 gradually tapered Severe withdrawal symptoms: Initial 2 capsules (trial dose) Day 0 1 to 2 capsules 2 hourly until sustained symptom resolution (day X) depending on response to initial trial dose Day X to end gradually tapered

1

1

Reference	Study type, evidence level, intervention	Comparison
Symptom-triggered versus routine hospital practice		
JAEGER 2001[34] Retrospective chart analysis 3	Symptom-triggered N=84 CIWA-Ar administered every one to two hours CIWA-Ar ≥ 10: chlordiazepoxide 50 to 100 mg starting dose and then repeated until 'CIWA-Ar score began to decline'	Usual care N=132 'Empirical' dosage usually on a tapering fixed-dose or with as-needed doses at the discretion of medical staff
REOUX 2000[35] Retrospective chart analysis 3	Symptom triggered N=26 (inpatient alcohol unit) CIWA-Ar administered one hour after being medication Score: ≥ 10 30 mg oxazepam or 50 mg chloridazepoxide ≤ 9 no medication	Non-protocol based detoxification N=14 (general medication ward [N=6] or inpatient psychiatry unit [N=8]) Medication ordered on a scheduled plus PRN (5/8 [62%]) or PRN only (3/8 [38%])

2

Reference	Study type, evidence level, intervention	Comparison
Front-loading dose versus fixed-dosing		
DAY 2004[36] RCT 1+	Front-loading N=11 CIWA-Ar administered every 90 minutes Score: ≥ 11 diazepam 20 mg ≤ 10 no medication Assessment/medication discontinued when score ≤ 10 on two consecutive occasions	Fixed-dose N=12 30 mg chloridazepoxide every six hours on the first day, with dose tapering to zero according to a defined regimen over a 10-day period. 20 mg chloridazepoxide every 6 hours if required. The CIWA-Ar was administered to all patients twice daily prior to the administration of the medication for the first ten days of the period of admission
JAUHAR 1999[37] RCT 1+	Front-loading N=11 Diazepam 40 mg once daily plus three placebo tablets Dose reduced over eight days Modified alcohol withdrawal chart administered	Fixed-dosing N=9 Chlodiazepoxide 80 mg four times daily Dose reduced over eight days Modified alcohol withdrawal

Reference	Study type, evidence level, intervention	Comparison
	four times daily Rescue medication: Oxazepam 20 mg	chart administered four times daily Rescue medication: Oxazepam 20 mg
MANIKANT 1993[39] RCT 1+	Front-loading N=20 CIWA-Ar administered every 90 minutes Score: CIWA-Ar 10 diazepam 20 mg	Fixed-dosing N=21 Diazepam 60, 40, 20, 20, 10 and 10 mg from day 1 to 7 respectively
WASILEWSKI 1996[38] Prospective cohort 2+	Front-loading N=51 CIWA-Ar administered every one to two hours Score: ≥ 11 diazepam 10 to 20 mg ≤ 10 no medication	Fixed-dosing N=45 Diazepam (N=43) 20 to 80 mg, Haloperidol (N=29) 5 to 30 mg Other medication included: Promethazine Hydroxyzine Clomethiazole Perazine Chlorpromazine Oxazepam

One retrospective case series looked at patients treated with front-loading diazepam who were given subsequent doses of diazepam with (N=133) or without (N=117) reference to the CIWA-Ar. The CIWA-Ar was administered hourly 'during the early stages of withdrawal' and then on an as-needed basis. If the score was greater than 10, 20 mg diazepam or 100 mg chlordiazepoxide were administered. In the comparison group patients were given additional medication without reference to the CIWA-Ar (the decision whether to use the scale was left to the staff i.e. non random) [41].

Level 3

Part b

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?

No papers were identified for the question.

2.3.3 Clinical Evidence Statements

Symptom-triggered versus fixed-dosing regimen

A summary of the results is presented in the table Table 2-5 below.

Overall, symptom-triggered dosing was associated with significantly lower doses of benzodiazepines than fixed-dosing [32] and with a shorter treatment duration and importantly without an increase in the incidence of seizures or delirium tremens [30]; [31]; [33]. One study reported that the difference in the amount of medication received between the two regimens was dependent on CIWA-Ar score at day one (the higher the initial score the greater the difference)[32].

Level 3

Despite decreased doses of medication with symptom-triggered compared with fixed-dosing, the former were not associated with an increase in the severity of withdrawal during treatment as indicated by the non-significant differences in number and amount of 'as-needed' or rescue medication required [30]; [31]; or co-medication [33].

Level 3

There were no significant differences in the number of patients reporting 'health concerns', for example discomfort [31] or depression [30] when comparing symptom-triggered with fixed-dose regimen (not significant). One study reported no significant differences between symptom-triggered with fixed dose regimen on the Medical Outcomes Study Short-Form Health Survey (MOS SF-36) when assessed at day three (physical functioning 91.9 [SD11.32] versus 84.2 [19.04]; p<0.01; vitality (59.6 [19.03] versus 55.2 [21.51]; ns; energy 67.0 [17.37] versus 66.3 [21.94]; ns)

Level 1++

One study reported significantly more protocol errors, for example, dose inconsistent with CIWA-Ar score or a mixture of scheduled doses and those based on assessment in the symptom-triggered group compared to the fixed-schedule dosing (18 versus 8%; p<0.05)[32].

Level 2++

Table 2-5. Summary of results.

Study	Total amount of medication	Duration of treatment	Severity of alcohol withdrawal	Incidence of seizures	Incidence of DTs
SAITZ 1994[31]	Median 100 (IQR 0 to 400) versus 425 (350 to 750) mg chlodiazepoxide ↓ symptom versus fixed (p<0.001)	Median 9 (IQR 0 to 43) versus 68 (64 to 73) hour ↓ symptom versus fixed (p<0.001)	Highest CIWA-AR score 11 (SD5) versus 11 (5); MD 0; 95%CI -1.85 to 1.85; p=1.0)	N=0	N=0
DAEPPEN 2002[30]	Mean 38 (81.7) versus 231 (29.4) mg oxazepam (MD -193.9; 95%CI -228.8 to	Median 20 (24.5) versus 63 (5.4) hour	Mean CIWA-Ar score	N=1 symptom-triggered	N=0

Study	Total amount of medication	Duration of treatment	Severity of alcohol withdrawal	Incidence of seizures	Incidence of DTs
	-159.0; p<0.00001) ↓ symptom versus fixed	↓ symptom versus fixed p<0.001)	Day 1 8.1 (SD5.8) versus 5.5 (3.7) (MD2.6; 95%CI 0.02 to 5.18; p=0.05) Day 3 4.2 (3.9) versus 2.7 (2.7) (MD1.5; 95%CI -0.27 to 3.27; p=0.10)		
WEAVER[32]	29 mg versus 100 mg lorazepam ↓ symptom versus fixed (p<0.0001)[1]	Not reported	Not reported	Not reported	Not reported
LANGE-ASSCENFELDT 2003[33]	Median 4352 (4589) versus 9921 (6599) mg clomethiazole ↓ symptom versus fixed (p=0.0004)	Median 4.2 (SD2.9) versus 7.5 days (3.3) ↓ symptom versus fixed (p=0.0003)	Not reported	N=1 symptom triggered	None reported

↓ denotes significant decrease ↑ denotes significant increase

[1] Protocol by CIWA-Ar interaction (see text for details)

Symptom-triggered versus routine hospital practice

In one retrospective case series 15/26 (58%) patients who received symptom-triggered dosing did not reach the threshold required to receive medication and 3/14 (21%) in the non-protocol group (PRN medication ordered by not administered) [35]. In the other retrospective case series 88% of patients receiving the symptom-triggered protocol and 82% on the fixed-dose/ as-needed protocol were prescribed benzodiazepines [34].

Level 3

►***Medication***

One study reported significant differences in favour of the symptom-triggered compared with the routine hospital practice with respect to mean number of doses of medication (1.7 [SD3.1] versus 10.4 [7.9], MD-8.7;95%CI -11.2 to -6.2; p<0.00001); the total amount of medication (82.7 [153.6] versus 367.5 [98.2] mg, MD -284.8; 95%CI -363.1 to -206.5; p<0.00001); but not the duration of medication use (10.7 [20.7] versus 64.3 [60.4] hours; MD-49.7; 95%CI -101.2 to 1.76; p=0.06) [35].

Level 3

In contrast, the study on medical in-patients reported no significant differences between those patients on symptom-triggered dosing compared with 'usual care' (a fixed-dose/ as-needed protocol) for the duration of treatment (mean 55.5 [SD54.5] versus 44.9 [49.6] hour; MD10.6; 95%CI -17.9 to 39.1; p=0.47); the proportion of patients prescribed benzodiazepines (74/84 [88%] versus 108/132 [82%]; RR1.08 [0.96 to 1.20]; p=0.20) ; or the mean total amount (mg) of benzodiazepines prescribed (20.1 [SD20.7] versus 20.1 [29.7] MD0.00; 95%CI -6.73 to 6.73; p=1.00) [34].
Level 3

►***Complications***
One study reported that no patient developed DTs or experienced a seizure [35].
Level 3

One study reported that symptom-triggered compared with 'usual care' was most effective at reducing the incidence on DTs in those patients without a prior history of DTs (17/84 versus 9/132; RR2.97; 95%CI 1.36 to 6.35; p=0.005). In those with a prior history of DTS the rates were 39% and 40% respectively (p=0.03 for the interaction between the intervention and prior history of DTs) [34].
Level 3

Loading-dose versus fixed-dosing

A summary of the results is presented in the table Table 2-6 below.

Three of the studies reported reduced total amounts of medication in patients treated with front-loading compared with fixed-dosing [36]; [39]; [38], although only one performed statistical analyses [36]. Two studies reported no significant differences in severity of alcohol withdrawal measured using the CIWA-Ar [39] and a scoring system developed within the hospital [37]
Level 2+

In patients presenting with alcohol dependence with a history of DTs [36] or with alcohol withdrawal syndrome presenting with DTs[38], front-loading compared with fixed-dosing was associated with a significantly reduced duration of DTs.
Level 2+

Owing to a low incidence rate of seizures, none of the studies performed statistical analyses on the data. However, all of the reported seizures were in the front-loading groups [36]; [39]; [38].
Level 2+

Front-loading was not associated with any significant differences on a measure of patient satisfaction [36]. Nursing staff reported that patients in the front-loading group were less sedated throughout the detoxification period and this enabled them to participate in psychological group work earlier than those in the fixed-dosing group [36].
Level 1+

Table 2-6. Summary of results.

Study	Total amount of medication	Duration of treatment	Severity of alcohol withdrawal	Incidence of seizures	Incidence of DTs
DAY 2004[36]	222 versus 700 mg chlrodiazepoxide equiv. (p<0.001) ↓ front loading versus fixed	Mean 8 versus 242 hours (p<0.001)↓ symptom versus fixed	Not reported	N=1 front loading	N=0
JAUHAR 1999[37]	NR	NR	NS	N=0	N=0
MANIKANT 1993[39]	Mean 67 versus 200 mg diazepam loading dose versus fixed dose (no analysis reported)	Not reported	Mean CIWA-Ar score NS	Not reported	Not reported
WASILEWSKI 1996[38]	Mean 87 (SD47.2) versus 1784 (1800) diazepam mg (MD -1697;95%CI -2235 to -1159; p<0.00001) (per treatment) ↓ front loading versus fixed	6.9 (4.8) versus 33.8 (25.7) hours (MD 26.9; 95%CI -34.7 to -19.1; p<0.0001) ↓ front loading versus fixed	Not reported	N=5 front loading versus N=2 fixed dose	All patients presented with DTs

Symptom-triggered bolus therapy (bolus group) versus continuous infusion

In the study on surgical intensive care patients who developed alcohol withdrawal, the results indicated that bolus-titrated therapy compared with infusion-titration led to a reduction in medication, incidence of intubation and pneumonia and duration of ITU stay (see table Table 2-7 below) [40].

Level 1+

The daily mean CIWA-Ar remaining elevated for a significantly longer period in patients and the duration of AWS was significantly shorted than in the bolus titrated compared with the infusion titrated group (both $p \leq 0.01$).

Level 1+

Table 2-7. Summary of results.

	Bolus titrated	Infusion titrated	P value
Outcome			
Medication (total amount mg)			

flunitrazepam clonidine haloperidol propofol (rescue)	70 (12.5 to 143.9) 1270 (1050 to 4768) 180 (80 to 554) 6 (2.2 to 15.1)	162 (91.4 to 807.0) 61098 (7188 to 147384) 1713 (270 to 3288) 9 (1.4 to 21.5)	p≤0.01 p≤0.01 p≤0.01 p=0.03
Intubation Incidence (%) Duration (days)	 15/23 (65) 6 (3 to 8)	 19/21 (90) 12 (5 to 20)	 P=0.05 p≤0.01
Length of ITU stay (days)	8 (5 to 10)	14 (7 to 25)	p≤0.01
Incidence of pneumonia (%)	9/23 (39)	15/21 (71)	p≤0.01

Front-loading plus CIWA-Ar compared with front-loading alone

Patients treated with reference to the CIWA-Ar received significantly less diazepam (median total dose 50 mg diazepam equivalent versus 75 mg, p=0.04) and a significantly greater proportion received low dose treatment (< 20 mg diazepam) (44/133 [25%] versus 25/117 [21%], p=0.05) in comparison with those treated without reference to the CIWA-Ar. There was no significant difference between the two groups with respect to mean length of stay (3.9 [SD2.2] versus 4.3 [2.4]; MD -0.40; 95%CI-0.97 to 0.17; p=0.17). One patient in each group developed delirium tremens and two patients in the group treated with reference to the scale developed seizures [41].

Level 3

2.3.4 Health Economic Methodological Introduction

No cost-effectiveness analysis was identified comparing treatment regimen for use in people with acute alcohol withdrawal (AAW).

The clinical evidence review showed that the symptom-triggered dosing regimen of benzodiazepines was associated with significantly lower doses of benzodiazepines[32] and shorter treatment duration compared to a fixed-dosing regimen[30,31,33]. A quality of life assessment found that a symptom-triggered dosing regimen improved patients' physical functioning compared to the fixed-dosing regimen (p<0.01)[30].

There are different cost implications associated with each type of dosing regimen. In addition to the difference in drug cost, the duration of treatment could have a large impact on the hospital length of stay and related costs. Similarly, each dosing regimen has different training and implementation implications and demands different amount of staff resource (to assess and monitor patients).

We undertook our own economic evaluation of symptom-triggered versus fixed-dose acute alcohol withdrawal (see A.3 for the full analysis).

2.3.5 Health Economic Evidence Statements

The objective of the economic analysis undertaken was to assess the cost-effectiveness of the fixed-schedule dosing regimen of benzodiazepines or clomethiazole, compared to a symptom-triggered dosing regimen, for the in-hospital management of patients with AAW in England and Wales. This economic analysis had mainly considered the experience of implementing and using the symptom-triggered regimen in the Addenbrooke's Hospital (Cambridge), the Huntercombe Centre (Sunderland), and the Royal Liverpool and Broadgreen University Hospital Trust. Four cost-effectiveness analyses were conducted, each based on a different clinical study comparing the symptom-triggered regimen with the fixed-dosing regimen. Two populations of patients were considered: patients with AAW admitted for the treatment of this condition alone; and patients with AAW admitted for a co-morbid medical condition. The economic modelling of the three clinical studies on patients admitted for AAW only (Deappen 2002[30], Saitz 1994[31], Lange-Asschenfeldt 2003[33]) considered the difference in length of hospital stay, which was significantly lower in the symptom-triggered arm of all three studies (see A.4 for details). In the Weaver study[32] (where patients were admitted for a co-morbid condition) there was no difference in the length of hospital stay between the trial arms as the co-morbid condition determined the length of hospital stay. The health outcome considered for this analysis was the Quality-Adjusted Life Year (QALY). This analysis was conducted from an England and Wales NHS perspective, with a time horizon extending to the end of the hospital admission.

None of the studies measured utility (health-related quality of life on a zero-one scale) but one study[30] employed the SF-36. We therefore derived mean utilities for each regimen by applying the SF-6D algorithm[42] to the original patient-level SF-36 data from this study [30]. The difference in utility scores between the cohorts was modest (0.0194) and non-significant (95% CI, -0.00972 to 0.4843; p=0.19). The Daeppen study[30] assessed health-related quality of life (SF-36) at three days post start of treatment and asked the patients to judge their health-related quality of life over the past three days for both the symptom-triggered and the fixed-dosing cohorts. QALYs were calculated by multiplying the utility score by the three days' duration for each arm. The Daeppen QALY gain was applied to the other studies.

Four categories of cost were considered in this analysis: drug treatment; hospitalisation; staff time for a nurse monitoring a patient with AAW; and the cost of implementing the symptom-triggered regimen. The cost of staff time was calculated by multiplying the average hourly cost of an NHS nurse by the time a nurse would be in contact with the patient. The amount of time a nurse is in contact with the patient was determined by the assessment schedule used by the nurse monitoring the patient and the number of minutes required to conduct each assessment. The assessment schedule assumptions used to calculate the staff time cost were based on schedules used in the clinical studies and in a selection of hospitals in England and Wales. The implementation cost was calculated considering that the training for staff is conducted in-house.

For the base-case analysis, in addition to a deterministic analysis (where cost and effect variables were analysed as point estimates), a probabilistic analysis was undertaken applying probability distributions to each model parameter and presenting the empirical distribution of the cost-effectiveness results. Deterministic sensitivity analyses

were performed to assess the robustness of the results to plausible variations in the model parameters: one-way sensitivity analyses involved varying the treatment cost, the hospitalisation cost, and the staff time cost; scenario sensitivity analyses varied the staff time cost (using alternative scenarios of assessment schedule and also varying the time a nurse is in contact with a patient for one assessment).

Deterministic results of the base-case analysis of the four cost-effectiveness analyses found the symptom-triggered regimen dominates the fixed-dosing regimen (it was more effective and less costly – refer to Table 2-8). The deterministic sensitivity analysis showed the conclusions of the base-case analyses are robust as the symptom-triggered option always remains dominant (cost-saving) or cost-effective (Table 2-8). The probabilistic results of the base-case analysis are in agreement with the deterministic results, showing that using a symptom-triggered regimen is cost-saving for treating patients admitted for AAW and those admitted for a co-morbid condition compared to a fixed-dosing regimen (Table 2-9). However, the probability of cost-effectiveness is quite low, reflecting the lack of significance in the difference in utility scores in the Daeppen trial (p=0.19).

The results were most sensitive to the assumptions about time spent per assessment. In the Weaver analysis (patients with AAW admitted for treating a co-morbid condition), if nurses spend more time on the symptom-triggered assessments than on the fixed-dosing assessments, then the symptom-triggered dosing regimen is likely to be no longer cost-saving. If the difference is more than 4 minutes per assessment, then symptom-triggered dosing regimen is no longer cost-effective (it costs more than £20,000 per QALY gained).

Table 2-8. Deterministic results.

Deterministic results				
	Patients admitted for treating AAW			Patients admitted for treating a co-morbid condition
Analysis	**Daeppen**	**Saitz**	**Lange-Asschenfeld**	**Weaver**
Base case analysis				
	Dominant (£398)*	Dominant (£551)*	Dominant (£723)*	Dominant (£27)*
Sensitivity analysis				
Remove hospitalisation cost	Dominant (£6)*	Dominant (£13)*	Dominant (£2)*	n/a
Using other drug 1	Dominant (£395)*	Dominant (£557)*	n/a	Dominant (£54)*
Using other drug 2	n/a	n/a	n/a	Dominant (£16)*
Inpatient cost £254 per day	Dominant (£461)*	Dominant (£637)*	Dominant (£838)*	n/a
Inpatient cost £271 per day	Dominant (£491)*	Dominant (£679)*	Dominant (£894)*	n/a
No. of assessment (favour S-T)	Dominant (£408)*	Dominant (£559)*	Dominant (£752)*	Dominant (£43)*
No. of assessment (favour F-D)	Dominant (£379)*	Dominant (£544)*	Dominant (£698)*	Dominant (£2)*

Nurse cost - Band 6	Dominant (£399)*	Dominant (£554)*	Dominant (£723)*	Dominant (£29)*
Time per nurse assessment	Dominant (£398)*	Dominant (£551)*	Dominant (£723)*	ICER = £7,489/QALY**
Probabilistic results				
Base-case analysis	Dominant (£396)*	Dominant (£563)*	Dominant (£735)*	Dominant (£29)*

* The symptom-triggered regimen is more efficient and *less* costly compared to the fixed-dosing regimen (total cost saved per patient using the symptom-triggered regimen is presented).

** The symptom-triggered regimen is more effective and *more* costly compared to the fixed-dosing regimen; the Incremental Cost-Effectiveness Ratio (ICER) is presented (which is below the NICE threshold of £20k/QALY gained).

Table 2-9. Probabilistic results.

Probabilistic results		
Analysis	**Incremental Net Monetary Benefit – £20,000/QALY (using symptom-triggered regimen compared with fixed-dosing)**	**Probability of symptom-triggered being cost-effective at £20,000/QALY**
Daeppen[30]	£1,683	63%
Saitz[31]	£1,581	62%
Lange-Asschenfeldt[33]	£1,879	63%
Weaver[32]	£1,128	59%

According to the results presented, the implementation and use of a symptom-triggered dosing regimen in patients with AAW in hospitals in England and Wales is cost-effective for the NHS, in both assessed populations of patients (those patients admitted for AAW treatment and those admitted for a co-morbid condition). The results of the four economic analyses, each based on a different trial, are in agreement, even considering the heterogeneity of trial results (drug dose and duration of treatment).

Results of the analyses conducted on the population of patients admitted for AAW treatment are mainly driven by the hospitalisation cost saved from the reduced length of hospitalisation using the symptom-triggered regimen. Results of the analyses conducted on the population of patients admitted for a co-morbid condition are mainly driven by the staff time cost saved using the symptom-triggered regimen. The sensitivity analysis illustrates the robustness of the results, even considering the small difference in QALYs between the compared regimens.

It was necessary to make some assumptions when developing this economic analysis and these were based on the clinical experience of GDG members with the aim of reflecting current medical practice. The assessment schedule assumptions used to calculate the staff time cost were based on schedules used in the clinical studies and in a selection of hospitals in England and Wales. For the base-case analyses, determining the assessment schedule for fixed-dosing regimen was straight forward as all protocols

proposed were similar. As there was variability in the assessment schedules in the symptom-triggered protocols used in the clinical trials, agreeing the frequency of monitoring to use in the base case was more problematic. The commonly used symptom-triggered assessment schedule in the Addenbrooke's Hospital (Cambridge) is every hour for 6 hours, then every 2 hours for 18 hours, then every four hours; in the Huntercombe Centre (Sunderland), 10 assessments in the first 24 hours and then 4 hourly; and in the Royal Liverpool and Broadgreen University Hospital Trust, every hour for 12 hours then every 4 hours. The latter was used in base-case analyses and is considered to be the most conservative (i.e. least favourable to the symptom-triggered dosing regimen). The Huntercombe Centre regimen was used in the scenario favouring symptom-triggered option in the deterministic sensitivity analysis as this was the least intensive of the symptom-triggered schedules. The scenario favouring the fixed-dosing regimen is a hypothetical scenario that uses an increased number of assessments than what we believe would be usual for current practice. Even in this scenario, the symptom-triggered dosing regimen remains cost-effective.

The results of the analysis conducted on patients admitted for a co-morbid condition are sensitive to how long a health-care worker spends with a patient each assessment. If the health-care worker spends longer than four minutes extra per assessment using the symptom-triggered regimen compared to using the fixed-dosing regimen, then the symptom-triggered option is no longer cost-effective. While it is unlikely that a competent nurse would ever spend longer than five minutes on each assessment, this highlights the need for effective training prior to implementing the symptom-triggered regimen in a service.

The cost of training nurses and implementing the symptom-triggered regimen was marginal and removing this cost did not affect the results of the analyses.

2.3.6 Evidence to recommendations

The clinical evidence for the front-loading versus fixed-schedule dosing studies was of lower quality (particularly with regard to sample size) compared to the evidence examining symptom-triggered versus fixed-schedule dosing. Therefore, the GDG agreed there was insufficient evidence to recommend front-loading dosing regimen at this time.

Overall, symptom triggered dosing is associated with significantly lower doses of benzodiazepines and with a shorter treatment duration without an increase in the incidence of seizures or delirium tremens. Despite decreased doses of medication with symptom-triggered compared with fixed-dosing regimen, the former regimen were not associated with an increase in the severity of withdrawal during treatment as indicated by the non-significant differences in number and amount of 'as-needed' or rescue medication required.

Health economic evidence suggests that symptom-triggered regimen is also cost-effective.

The GDG reviewed the evidence and noted that in the two studies comparing symptom-triggered with fixed dosing regimen and the one study comparing front-loading with fixed dosing regimens which also measured patient-reported outcomes (e.g. discomfort and depression), these data were gathered at the end of the treatment. Therefore, these reports may not have been as accurate as if the information was reported during treatment.

The majority of studies were obtained from predominantly male populations admitted to specialist addiction services. There was only one study which reported on the management of withdrawal in a general medical ward setting. The GDG have therefore recommended that further research on the most appropriate regimen is carried out specifically in the acute setting of general hospitals with patients admitted for an unplanned medically assisted withdrawal from alcohol.

The trials reviewed provide evidence from both planned and unplanned medically-assisted alcohol withdrawal episodes. There was debate amongst the members of the GDG as to whether data from planned episodes could be extrapolated to unplanned episodes. It was considered that while the symptoms and signs of withdrawal in the two populations may be similar, the patients admitted in unplanned withdrawal may have a more severe syndrome at presentation than those with planned withdrawal and, as a result, may be more likely to progress to a seizure or the DTs. In addition, the setting of planned and unplanned withdrawal from alcohol is often different. As a result, people presenting for planned withdrawal are more likely to be managed by dedicated alcohol workers with specific sets of skills, while those presenting in withdrawal to a general hospital are more likely to be managed by doctors and nurses with more general skills.

The GDG discussed their concerns about the suitability of recommending a treatment regimen that has been proven to be successful in a certain setting (specialist addition services) and recommending it in another setting where the conditions are likely to be different and the people required to deliver the treatment often do not have the necessary skills (general medical hospital ward). Nevertheless, because of the paucity of studies in the acute setting and the apparent benefits of a symptom-triggered regimen in the controlled setting, it was ultimately decided that the recommendation should reflect this apparent superiority. It was agreed that a caveat regarding the facilities for assessment and monitoring should be included in the recommendation.

All of the evidence for symptom-triggered versus fixed-schedule regimens used the CIWA-Ar to measure the severity of alcohol withdrawal. While this provided consistency between the studies, it did not allow us to compare the CIWA-Ar with other assessment tools. In addition, there were no studies that compared the use of CIWA-Ar to supplement clinical judgement with clinical judgement alone.

The GDG noted that symptom-triggered dosing regimen require people to be closely monitored for changes in the severity of their withdrawal. In addition, specialist expertise is required, that is health care workers with clinical knowledge to identify signs and symptoms that imply a change in severity of withdrawal. The GDG considered

that in specialist units this can be achieved through experience, but that the introduction of a symptom-triggered regimen into a general medical setting may need to include training in the use of a valid and reliable tool (for example, the CIWA-Ar) to supplement clinical judgement. This question will be further assessed when discussing the aspects of supportive care required to manage patients with acute alcohol withdrawal.

2.3.7 Recommendations

R7 For people in acute alcohol withdrawal, follow a symptom-triggered regimen for drug therapy if 24 hour assessment and monitoring are available.

2.3.8 Research Recommendations

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 usual care pathways with no input from an alcohol nurse specialist?

2.4 Management of Delirium Tremens

2.4.1 Clinical Introduction

Delirium tremens (DT) is an extremely distressing condition, and patients may represent a danger to themselves or others. Untreated, it has a significant mortality associated with severe sympathetic over-activity. DTs occur primarily under two circumstances (i) when a patient with established withdrawal or who is at risk of developing withdrawal receives treatment which is ineffective (break through) or (ii) when a patient presents late with established symptoms having not received treatment. There is no consensus on the best pharmacological agent to manage this condition.

The clinical question asked, and upon which literature searching was undertaken was:

"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?"

2.4.2 Clinical Methodological Introduction

No relevant papers were identified for this question.

2.4.3 Health economic methodological introduction

No relevant economic evidence was identified that assessed the cost-effectiveness of using benzodiazepines, neuroleptic agents, and other agents as treatment for people with delirium tremens. GDG members received a list of costs for the different drugs assessed by the clinical question, in association with the specific dosages as recommended for use in England and Wales[28,43].

2.4.4 *Health economic evidence statements*

The cost of oral lorazepam, identified by the GDG as potential first-line treatment, is low (few pence per dose)[43]. If symptoms are severe or oral medication is declined, parenteral lorazepam, haloperidol or olanzapine are options. Parenteral olanzapine is more expensive than lorazepam and haloperidol (£3.48 per olanzapine dose (10mg), versus few pence per dose for lorazepam and haloperidol)[43].

2.4.5 *GDG discussion*

The GDG considered the clinical and cost-effectiveness evidence for the treatment of delirium tremens under circumstances where the treatment for withdrawal prescribed has not been effective (break through) or the patient presents with established symptoms having not received treatment. The clinical evidence review found no papers to inform the discussion so any recommendations are based on experience and consensus.

The GDG noted that people experiencing delirium tremens are often distressed. It is important to provide treatment urgently. As it is unclear when the initial management regimen will become effective, the clinician will need to administer a drug that will work until the point the initial regimen takes over. As there was no clinical evidence showing preference for one agent over another the GDG agreed on consensus that symptoms should be relieved using oral lorazepam in the first instance. If symptoms are severe or oral medication is declined, parenteral lorazepam, haloperidol or olanzapine may be used.

The GDG felt that olanzapine has a better side effect profile than lorazepam and haloperidol, especially in high doses, which is the case here. In spite of the additional cost associated with parenteral olanzapine compared to lorazepam and haloperidol, the overall cost-impact of giving this treatment is likely to be small because this indication often only required a single dose, and the number of patients that may required this treatment are few, especially if used as a second-line treatment for agitation.

2.4.6 *Recommendations*

R8 If delirium tremens develops in a person during treatment for withdrawal, review their management.

R9 Offer oral lorazepam to treat delirium tremens in the first instance. If symptoms persist or oral medication is refused, give parenteral lorazepam, haloperidol or olanzapine.

2.5 TREATMENT FOR SEIZURES

2.5.1 CLINICAL INTRODUCTION

One of the important goals of treatment in acute alcohol withdrawal is the prevention of seizures. In fact, one of the outcome measures used to determine the success of a treatment regimen is the frequency of seizures in the population treated. Guidelines for the prevention of seizures are therefore the same as the guidelines for the management of acute alcohol withdrawal. Good management will reduce the incidence of seizures, but guidance is still required to manage seizures should they occur. This can happen during a planned or unplanned medically assisted withdrawal from alcohol with the frequency reported as around 8%. Seizures may also be the presenting feature of alcohol withdrawal when a dependent drinker has reduced their alcohol consumption in the community.

The primary goal of treatment is initially to terminate the seizure. Fortunately, alcohol-withdrawal seizures are almost universally self-limiting, and, most commonly, patients present after the event. In this situation the goal is to prevent further seizures and allow the continued management of the other features of alcohol withdrawal as recommended above. This is the most common clinical scenario.

Although several different benzodiazepines and anticonvulsants are in regular clinical use, the optimum management of this common problem is still unclear.

The clinical question asked, and upon which literature searching was undertaken was:

> *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?*

2.5.2 CLINICAL METHODOLOGICAL INTRODUCTION

One meta-analysis (N=4 placebo-controlled randomised trials) was identified addressing the management of recurrent seizures in patients with acute alcohol withdrawal [44].

Level 1+

One trial (N=188) [45] in the meta-analysis compared lorazepam 2mg with saline in patients presenting to the emergency department after a witnessed generalised seizure. Patients were observed for a minimum seizure-free period of 6 hours.

Level 1+

Three trials in the meta-analysis (N=252 patients in total) compared phenytoin with placebo [46]; [47]; [48]. Two of the studies observed patients for a minimum seizure-free period of 6 hours [47]; [48] and in the remaining study for 12 hours [46]

Level 1+

All of the studies recruited patients who presented to an emergency department with a seizure thought to be related to acute alcohol withdrawal and were therefore not on medication for treatment of this condition. The question addressed here is how to manage patients who have been started on a treatment regimen for acute alcohol withdrawal but who then have a seizure presumed to be withdrawal-related.

2.5.3 Clinical Evidence Statements

Lorazepam but not phenytoin is effective in the management of withdrawal seizures compared with placebo (see table below for details of the individual studies in the meta-analysis) [44]. The number of patients needed to be treated with lorazepam to prevent one seizure is five (95%CI 3.2 to 8.5)[a]. See table 2-10 for a summary of results.

Level 1+

2-10. Summary of results.

	Observation time (hours)	Number of patients developing seizures		Risk difference (cases of seizures per 100 patients)	95% CI
Study		**Intervention**	**Placebo**		
Benzodiazepines versus placebo				-21.4 treated with benzodiazepine	-31.7 to -11.7
D'ONOFRIO et al. 1999[45]	6	3/100 (3%)	21/86 (24%)	-0.7 treated with ACs	-10.4 to 9
Anticonvulsants versus placebo					
ALLDREDGE et al. 1989[46]	12	6/45 (13%)	6/45 (13%)	RR1.00 P=1.0	0.35 to 2.87
CHANCE 1991[47]	6	6/28 (21%)	5/27 (19%)	RR1.16 P=0.79	0.40 to 3.35
RATHLEV et al. 1994[48]	6	10/49 (20%)	12/51 (24%)	RR0.87 P=0.71	0.41 to 1.82

2.5.4 Health Economic methodological introduction

No relevant cost-effectiveness evidence was identified involving patients suffering from recurrent seizures, and the efficacy of anticonvulsant agents and benzodiazepines. GDG members received a list of costs for the different drugs appraised by the clinical literature review, in association with the specific dosages as recommended for use in England and Wales[27,28].

[a] The meta-analysis reports the NNT as -150 (95%CI 10 to -1)

2.5.5 *HEALTH ECONOMIC EVIDENCE STATEMENTS*

The cost of medications for treating patients with AAW is relatively low[27], and this treatment is given for a short period. The cost-impact related to this therapy is therefore likely to be small.

2.5.6 *EVIDENCE TO RECOMMENDATIONS*

The GDG discussed the difference between preventing seizures, treating a patient during a seizure and preventing recurrent seizures. It was noted that effective treatment of acute alcohol withdrawal will result in the prevention of seizures. As such, a seizure in a patient during treatment can be considered as a treatment failure. The GDG therefore agreed that it was important to emphasise the need to review a patient's treatment regimen if they develop a seizure as this may be due to a sub-optimal level of initial treatment.

Further discussion revolved around the issues of treating an acute seizure and preventing further seizures in those patients who present having had a seizure. The GDG noted that the evidence considered was obtained from people not receiving any treatment for acute alcohol withdrawal but who presented to Accident and Emergency following an initial alcohol withdrawal related seizure. In spite of this, the GDG thought that the evidence could be extrapolated to those patients that have had a seizure on a withdrawal regimen.

It is rare for an alcohol withdrawal seizure not to be self-limiting, so the clinical question had been posed to determine how to manage a patient who has had a seizure. Specifically, it had been posed to determine if benzodiazepines or anticonvulsants were efficacious in this clinical situation.

The evidence included a low quality meta-analysis with no assessment of individual study quality. The evidence did not report any adverse events or complications associated with lorazepam.

The D'Onofrio[45] study showed that lorazepam was superior to placebo in preventing further seizures. It was noted that this study excluded people after enrolment if they required treatment for moderate to severe withdrawal. As such, the GDG recognised significant limitations with the study as it does not reflect the population in the UK that usually needs treatment to prevent recurrent seizures.

The GDG considered it important that the three studies comparing phenytoin with placebo reported no significant differences in the incidence of recurrent seizures.

None of the evidence reviewed included people from the young adult and older adult populations.

2.5.7 *RECOMMENDATIONS*

R10 If alcohol withdrawal seizures develop in a person during treatment for withdrawal, review their management.

R11 In patients with alcohol withdrawal seizures, use a quick-acting benzodiazepine (such as lorazepam) to reduce the likelihood of further seizure if needed.

2.6 SUPPORTIVE CARE

2.6.1 *CLINICAL INTRODUCTION*

Patients who are alcohol dependent and therefore at risk of developing acute alcohol withdrawal (AAW) may have complex needs. They are likely to have experienced health problems leading to frequent attendance at acute hospitals, particularly accident and emergency departments[4]. It would seem both sensible and practical to ensure that when such patients present, health professionals in this setting have the necessary skills to manage their condition in an effective and timely manner. Such skills include the ability to detect alcohol dependence at an early stage in a presentation, and to accurately assess the severity of, or the risk of developing AAW.

It is recognised that the management of AAW varies according to the expertise available at the point of assessment. Early detection and prompt initiation of treatment is crucial as untreated AAW may progress to delirium tremens, which can be fatal in untreated patients. Death may result from respiratory and cardiovascular collapse or cardiac arrhythmias. As well as reducing mortality, accurate assessment and optimal treatment results in fewer complications, reduces progression to delirium, reduces the course and duration of AAW, and consequently reduces length of stay in hospital.

The scope of this guidance is to provide recommendations for the medical management of AAW. Thus, we need to determine if tools are available to assist in accurate assessment of the severity of alcohol withdrawal , if these tools are clinically effective, and who is best placed to utilise these tools in the development of effective care pathways.

The dedicated alcohol specialist nurse (ASN) is considered important in assessing patients and enhancing patient compliance and concordance, augmenting medical treatments and co-ordinating aftercare and follow-up. These factors have been demonstrated to be essential components of effective treatment. It is noteworthy that the recently revised version of CIWA-Ar, the CIWA-Ad, has been demonstrated to have good inter-rater reliability for use by nurses, the K-value for the entire AAS scale being 0.64[49].

The clinical question asked, and upon which literature searching was undertaken was:

1) 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?

2) Does the assessment and monitoring of patients with acute alcohol withdrawal improve patient outcomes?

2.6.2 CLINICAL METHODOLOGICAL INTRODUCTION

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?

One paper (N= 203) was identified. The study reported on patients under the care of all specialties, [and of] general and orthopaedic surgeons, who were identified as at risk of alcohol withdrawal within the first 24 hours of admission. The Clinical Institute Withdrawal Assessment (CIWA) score was used to determine frequency of monitoring (range one to four hourly), duration of monitoring and treatment based on a loading dose regimen [50].

Level 3

Does the assessment and monitoring of patients with acute alcohol withdrawal improve patient outcomes?

Papers were included if they compared outcomes before and after the implementation of a protocol, guideline or patient pathway that used a tool, scale or clinical judgement to assess and/or monitor patients with acute alcohol withdrawal.

An important methodological consideration is that the majority of studies changed the treatment regimen whilst simultaneously altering aspects of assessment and monitoring. Some studies also implemented an education/training programme. The large numbers of confounding variables make it impossible to identify precisely which of these different components were associated with changes in outcome. The results are reported as follows:

- One prospective case series (N=539 episodes) reported on factors associated with the incidence of seizures, hallucinations or delirium in patients in a general hospital who experienced alcohol withdrawal (only the factor 'delayed assessment' is reported here)[51].
  Level 3

- Four studies reported on patients at risk of, or with, alcohol withdrawal that were treated with reference to a rating scale compared to those that were treated without reference to a scale [52] [53] [13,54]. See table X below for methodological details.
  Level 3

- One study of patients with uncomplicated alcohol withdrawal, implemented a change from fixed-dose scheduling to a symptom-triggered regimen [55]. See Table 2-11below for methodological details.
  Level 3

- One study was included that reported on the inappropriate use of symptom-triggered dosing in medical and surgical patients admitted to a general hospital (N=124) [56].
  Level 3

- One study reported on patients with acute alcohol withdrawal admitted to intensive care unit [57]. See Table 2-11below for methodological details.
  Level 3

Table 2-11. Summary of included studies.

Study	Study type and number	Patient population and setting	Intervention	Comparison
Pletcher 2005[54]	Retrospective case series, N=500	Patients with alcohol-related discharge diagnosis (ICD-9) Setting: General hospital	Post-protocol, N=202 CIWA monitoring fixed dose scheduling for at risk or symptomatic patients with CIWA monitoring to allow for extra doses as-needed. Education campaign Standard order form	Pre-protocol, N=188 Fixed-schedule dosing without the use of standard monitoring
Repper-DeLisi 2008[52]	Retrospective case series 3, N=80	Patients with alcohol withdrawal alcohol consumption within two weeks of admission and/or	Post-pathway, N=40 Pathway developed to: Increase recognition of those at risk of withdrawal and to treat patients before they	Pre-pathway, N=40 Benzodiazepines at the discretion of staff, such as without a protocol

Study	Study type and number	Patient population and setting	Intervention	Comparison
		withdrawal or treatment for alcohol withdrawal during the index admission Setting: medical and surgical patients admitted to a general hospital	became symptomatic. Also, to facilitate aggressive treatment of alcohol withdrawal Assessment consisted of: CAGE, vital signs, alcohol history, withdrawal signs, delirium, risk factors. Treatment: fixed dose benzodiazepines Training and education program	
Hecksel 2008[56]	Retrospective case series 3, N=124 episodes	Patients who received symptom-triggered therapy according to the CIWA-Ar protocol Setting: Medical and surgical patients admitted to a general hospital	Appropriate symptom-triggered therapy	Inappropriate symptom-triggered therapy
DeCarolis 2007[57]	Retrospective case series 3 N=40	Patients admitted to a medical intensive care unit with a primary diagnosis of severe alcohol withdrawal	Protocol-treated patients N=24 (21 patients) Minnesota Detoxification Scale (MINDS) to	Non-protocol patients N=16 (15 patients) Patients treated according to physician preference; the standard local practice was administration of

Study	Study type and number	Patient population and setting	Intervention	Comparison
			monitor symptoms. Treatment: Lorazepam administered as intermittent intravenous doses, progressing to a continuous intravenous infusion according to the MINDS score Assessments performed every 15 minutes to 2 hours depending on MINDS scoreb	a continuous infusion of midazolam without a protocol
Stanley 2007[53]	Before and after retrospective case series 3	Patients at risk of alcohol withdrawal admitted to the surgery or internal medicine services	Guideline managed patients, N=106 The guideline comprised of: Symptom-triggered dosing schedule, guideline on how to manage a seizure or delirium and patients with specified comorbid conditions. Monitor using the Alcohol Withdrawal Scale type indicator every two to four hours according to score	Non-guideline managed patients, N=82 Prior to the guideline benzodiazepines were given around the clock and/or as needed and these vitamin supplements were commonly prescribed for patients with suspected or known alcohol abuse

Study	Study type and number	Patient population and setting	Intervention	Comparison
Foy 1997[51]	Prospective case series N=539	Patients with alcohol withdrawal Inclusion criteria (one or more of the following): 100g alcohol daily or more; admission with an alcohol-related diagnosis; previous documented alcohol withdrawal and still drinking; a blood alcohol level of 0.2% without impairment of consciousness, and who had an Alcohol Withdrawal Scale (AWS) ≥ 10	Alcohol Withdrawal Scale (AWS) – modification of the CIWA-A Loading dose diazepam 20 mg if: Two scores of 15 or more or one of 20 then consider treatment but the decision to treat, dose and technique was at the discretion of the treating team Timing of assessment If AWS ≥ 10 assess every two hours, if ≥ 15 then hourly	Whether a delay in assessment was associated with seizures, hallucinations and delirium
Wetterling 1997[13]	Prospective case series 3, N=387	Patients with long-standing alcohol dependence (DSM-IV) admitted for detoxification. Setting: psychiatric emergency ward	Symptom-based protocol, N=256 Alcohol Withdrawal Scale (AWS) derived from the CIWA-Ar. AWS administered every 2 hours Treatment protocol: Mild AWS – no medication Moderate AWS – carbamazepine	Non-protocol group (validation phase), N=131 Patients were treated without reference to a rating scale (no further details reported).

Study	Study type and number	Patient population and setting	Intervention	Comparison
			up to 900mg/day Severe AWS – clomethiazole.	
Morgan 1996[55]	Retrospective before and after time series/case series 3, N=197	Patients needing hospitalization to treat uncomplicated alcohol withdrawal syndrome. Setting: psychiatric unit	Post-pathway, N=56 Pathway for uncomplicated alcohol withdrawal incorporating the use of the CIWA-Ar Move towards symptom-triggered dosing but clinicians made decisions independently benzodiazepine prescribing One year after pathway implementation N=75 Pathway included a protocol for benzodiazepine dosing according to a symptom-triggered CIWA-Ar based schedule	Pre-pathway, N=66 No standard assessment scale. Implied that fixed-dosing scheduling used but not explicitly stated.
Jaeger 2001[34]	Retrospective case series 3 N=216 admissions	Patient with a discharge diagnoses of alcoholism, delirium tremens, alcohol withdrawal or alcohol	Symptom-triggered (Post implementation), N=84 CIWA-Ar administered	Usual care (Pre-implementation),N=132 'Empirical' dosage usually on a tapering fixed-dose or with as-needed doses at the

Study	Study type and number	Patient population and setting	Intervention	Comparison
		withdrawal seizures. Patients who received thiamine and benzodiazepines simultaneously. Setting: Patients on general medical wards	every 1 to 2 hours CIWA-Ar ≥ 10: chlordiazepoxide 50 to 100 mg starting dose and then repeated until 'CIWA-Ar score began to decline'	discretion of medical staff
Reoux 2000[35]	Retrospective case analysis 3 N=40	Patients with discharge codes for alcohol withdrawal, delirium tremens, drug withdrawal or alcohol hallucinosis Setting: Alcohol unit, medication ward, inpatient psychiatry unit	Symptom triggered dosing (CIWA-Ar), N=26 CIWA-Ar ≥ 10 30mg oxazepam or 50 mg chloridazepoxide CIWA-Ar administered hourly and continued to receive medication until the score dropped below 10.	Non-protocol based detoxification, N=14 Detoxification occurred in a general medication ward (N=6) or inpatient psychiatry unit (N=8) Protocol: Medication ordered on a scheduled plus PRN (5/8 [62%]) or PRN only (3/8 [38%])

2.6.3 Clinical Evidence Statements

One study reported on the use of a modified CIWA in the management of alcohol withdrawal in a general hospital [50].

Level 3

► ***Incidence of complications***

- 110/204 (54%) patients had a score of greater than 15 and received at least one dose of diazepam 20 mg.
  Level 3

- 15/93 (16%) of those patients who scored less than 15 received prophylactic treatment with at least diazepam 20 mg [50].
  Level 3

- 37/204 (18%) patients suffered complicated alcohol withdrawal reactions (N=4 seizures, N=33 confusion with or without hallucinations, N=0 hallucinations alone) [50].
  Level 3

- Scores were significantly higher in patients who developed complications (confusion, hallucinations or seizures) compared to those patients who did not develop complications (mean highest score 21.8 [SD1.2] versus 15.6 [0.55], MD6.10; 95%CI 5.67 to 6.53; p<0.00001) [50]
  Level 3

►***Prophylactic effect of treatment on different scores***

- Of the 110/204 (54%) patients who had scores greater than 1575 were treated of whom 11 developed severe withdrawal. In the 35 who were not treated, 21 (15% of 204) developed severe withdrawal. The relative risk of severe withdrawal in those remaining untreated was 3.72 (95%CI 2.85 to 4.85) [50]

Overall, the scale was reported as valuable at identifying patients in early withdrawal who need drug therapy to avoid complications. Table 2-12 below gives the relative risks for untreated patients according to the score on the modified CIWA [50].
Level 3

Table 2-12. Relative risks for untreated patients according to CIWA score.

	Complicated	Uncomplicated	RR untreated versus treated	95%CI
Score < 15 Untreated Treated	 5 0	 73 15	1.92	0.27 to 13.6
Score 16 to 20 Untreated Treated	 9 5	 12 17	2.74	1.06 to 7.05
Score 21 to 25 Untreated Treated	 7 4	 1 21	5.46	2.14 to 13.9
Score > 25 Untreated Treated	 5 2	 1 15	7.50	3.87 to 29.07

►***Timing of assessment & frequency of monitoring***

One prospective case series reported on the incidence of seizures, hallucinations and delirium and the risks associated with these events in patients with acute alcohol withdrawal admitted to a general hospital [51].
Level 3

A delay of greater than 24 hours before the first assessment was significantly associated with:

- any complication (25/52 [48%], OR [adj.] 4.0; 95%CI 2.7 to 7.6)
- delirium (20/52 [38%], OR [adj.] 8.1; 95%CI 3.7 to 17.7)
- hallucinations (18/52 [35%], OR [adj.] 3.2; 95%CI 1.6 to 6.0) [51].

Level 3

Patients (excluding those with complications on admission) whose monitoring was delayed were:

- three times more likely to have complications compared with those who were identified in the first 24 hours (25/52 [48%] versus 71/408 [17%]; RR2.76; 95%CI 1.94 to 3.93; p<0.0001) [51].

Level 3

Studies implementing protocols using fixed-dose regimen

►***Timing of assessment & frequency of monitoring***

One study reported that the implementation of a pathway was associated with a non significant increase in:

- the mean number of vital sign checks over three days (pre versus post 20.0 [SD12.5] versus 25.9 [17.1]; MD-5.90; 95%CI -12.46 to 0.66; p=0.08) [52].

Level 3

►***Medication dose***

The results of the studies varied with respect to changes in medication before and after the implementation of a 'fixed dose' pathway are presented in Table 2-13:

Table 2-13. Summary of results.

Medication dose		
Study and Outcome	**Pre versus Post pathway**	**P value**
Pletcher 2005[54] % treated with diazepam	49/188 (26%) versus 10/202 (5%)	5.26; 2.25 to 10.09; p<0.00001
% treated with any benzodiazepine	143/188 (77%) versus 152/202 (75%)	1.01; 0.90 to 1.13; p=0.85
% treated with lorazepam	120/188(64%) versus 131/202 (65%)	0.98; 0.85 to 1.14; p=0.83
% treated with chloridazepoxide	98/188 (52%)versus 91/202 (45%)	1.16; 0.94 to 1.42; p=0.16
Repper-DeLisi 2008[52] % of benzodiazepine administered as standing doses Days one, two and three	Approx Day one 56 versus 75 Day two 62 versus 82 Day three 64 versus 80	 <0.05 <0.01 <0.05

Medication dose		
Stanley 2007[53]		
% receiving drug therapy	9/82 (11%) versus 36/106 (34%)	RR0.32; 95%CI 0.17 to 0.63; p=0.001
		<0.01
Mean total lorazepam mg (range)	23.3 (0 to 186) versus 7.8 (0 to 58)	<0.01
Mean total clonidine mg	0.05 (0 to 1) versus 0.2 (0 to 6.6)	0.17
Mean total haloperidol mg	5.9 (0 to 129) versus 4.0 (0 to 106)	RR4.74; 2.68 to 8.38; p<0.0001
% discharged on tapered benzodiazepine therapy	44/82 versus 12/106	
Wetterling 1997[13]		
% receiving clomethiazole	64/132 (48%) versus 58/256 (23%)	RR2.14; 1.61 to 2.85; p<0.0001
Mean amount of applied dose of clomethiazole per patients mg	7680 (SD 8952) versus 5061 (2626)	MD 2619; 1058 to 4179; p=0.001

To summarise, fixed dose regimen pathways compared to hospital practice prior to the implementation of the pathway were associated with

- significantly fewer patients being treated with diazepam [54]
- a significantly lower proportion of benzodiazepines administered as a standing dose, days one to three [52]
- significantly more patients receiving drug therapy but with significantly lower doses of lorazepam and clonidine [53]
- significantly fewer patients discharged on tapered benzodiazepine therapy [53]
- significantly fewer patients receiving clomethiazole and at a lower mean dose per patient [58]

► ***Length of stay/duration of treatment***

Pre versus post-implementation:

- a significant *increase* in the length of stay when comparing pre and post implementation of pathway (median 3 [2 to 6] versus 4 [2 to 7] days [OR adj. 0% or percent increase 18% [95%CI0.9 to 37%]) and a similar finding was reported when comparing pre-pathway with a two year follow-up (median 3 versus 4 days; OR [adj) -3% (-14% to 8%) [54].
  Level 3

- a significant *decrease* in the duration of treatment (mean 3.8 [SD1.6] versus 2.7 [2.5] days; MD1.10; [95%CI 0.28 to 1.92; p=0.009]) [58].
  Level 3

One study reported:

- no significant difference in the length of stay when time periods before and after the implementation of pathway were compared (5.3 versus 3.9; not significant) [53] 5.4 (SD4.9) vd 4.0 (2.7); MD1.40; 95% (CI -0.33 to 3.13; p=0.11) [52].
  Level 3

►***Complications***

Pre- versus post-implementation:

- a significant increase in the proportion of patients who died (2.7 versus 3.5%); OR (adj) 2.1 (95%CI 1.0 to 4.6). A similar finding was reported when comparing pre-pathway with two years after pathway implementation (2.2 versus 3.3%; OR [adj] 1.2 [95%CI 0.6 to 2.4])/ [54]. Note: no explanation for this finding was identified.
  Level 3

- a significant decrease in the proportion of patients transferred to a higher level of care after the implementation of a pathway (22 versus 17%; OR [adj] 0.6 [95%CI 0.3 to 1.0])[54]
  Level 3

- a significant decrease in the incidence of delirium tremens (adjusted 52% versus 40%; p<0.05) [52];
  Level 3

There was no significant difference when comparing pre and post implementation of pathway for:

- the incidence of delirium tremens (41 versus 35%, OR [adj.] 1.2; 95%CI 0.8 to 1.9, ns) [54]; 27/256 (11%) versus 13/131 (10%); ns [58]
- the incidence of seizures (3.2 versus 3.5%, OR [adj.] 1 versus 0.9; 95%CI 0.3 to 3.0, ns)[54].
  Level 3

Protocol changing from a fixed-dose schedule to symptom-triggered prescribing in patients with 'uncomplicated alcohol withdrawal'

►***Medication dose***

One study reported that following the initiation of the pathway changing from a fixed-dose regimen to a symptom-triggered regimen (with no prescribing regime) followed by a symptom-triggered regimen with prescribing based on the CIWA-Ar score ('one year' after) there was:

- a significant decrease in the mean dose of benzodiazepine per episode as scheduled medication (diazepam equivalents) (74.6 [SD 92.7] mg to 31.4 [SD 47.5] mg after [RR43.20; 95%CI 17.6 to 68.8; p=0.009]), and to 9.9 (SD 32.2) 1 year after (RR64.7; 95%CI 41.2 to 88.2; p<0.00001) [55].
  Level 3

- Mean milligrams of benzodiazepine per episode-total (diazepam equivalents) significantly decreased from 95.3 (SD 100.2) diazepam equivalents (mg) to 47.5 (SD 56.6) after pathway initiated (RR47.8; 95CI 19.4 to 76.2; p=0.0010), and dropped further to 31.4 (SD 41.9) 1 year after (RR63.9;95%CI 37.9 to 89.9; p<0.00001) [55].
  Level 3

► ***Length of stay/duration of treatment***

The implementation of a clinical pathway for uncomplicated alcohol withdrawal incorporating the use of the CIWA-Ar to 'encourage' symptom-triggered dosing (after) and in a follow-up with a more prescriptive protocol for benzodiazepine dosing based on the CIWA-Ar resulted in:

- a non significant decrease significantly following initiation of pathway, from a mean 6.67 (SD 5.14) days before to 5.25 (SD 3.50) after (RR 1.42:95%CI -0.12 to 2.96; p=0.07), and a significant decrease to 4.31 (SD 2.96) days 1 year after (RR 2.36;95%CI0.95 to 3.77; p=0.001) [55].
  Level 3

ITU setting

► ***Medication dose***

One prospective case series looked at outcomes in patients with alcohol withdrawal delirium in patients admitted to ITU when treated with a symptom-driven benzodiazepine protocol versus non-protocol benzodiazepine infusions [57]
Level 3

The symptom-triggered protocol compared to the pre-protocol was associated with significantly:

- Less time to reach a Minnesota Detoxification Scale MINDS score of less than 20 (symptom control) (mean 7.7 [4.9] versus 19.4 [9.7]; MD -11.70;95%CI 16.26 to -7.14; p=<0.00001)
- Lower cumulative mean benzodiazepine dose (1044 [SD534] versus 1677 (937) lorazepam equivalent; MD-633; 95%CI -113.9 to -126.6; p=0.01).
- Less time receiving continuous-infusion benzodiazepine (52 [35] versus 122 [64] hours; MD -70; 95CI -104.34 to -35.66; p<0.0001) [57].
  Level 3

► ***Length of stay/duration of treatment***

- There was no significant difference in the mean length of stay when time periods before and after the implementation of a symptom-driven protocol were compared (15 [SD9] versus 11 [3] days;MD-4.00; 95%CI -8.57 to 0.57; p=0.09) [57].
  Level 3

► ***Complications***

Pre-protocol group:
There were 7 treatment-related complications (44%):

- N=3 intubations (N=2 due to over sedation)
- N=2 aspiration pneumonia
- N=2 diazepam IV extravasations.

Symptom-triggered group:
There were 6 treatment-related complications (25%) including

- N=2 intubations for acute respiratory failure
- N=2 propylene glycol toxicity in patients receiving high infusion rates of lorazepam.

Inappropriate use of symptom-triggered therapy

One study reported on the inappropriate use of symptom-triggered therapy in medical and surgical patients. Symptom-triggered therapy was deemed appropriate if the person has a history of recent alcohol abuse and has intact verbal communication (symptoms of withdrawal were monitored using the CIWA-Ar that depends on the ability to communicate) [56].

Level 3

- 60/124 (48%) patients met both inclusion criteria (drinking history and communication) for symptom-triggered therapy. Of the remaining 64, nine patients (14%) were heavy drinkers but had been unable to communicate; 35 patients (55%) did not have a recent history of heavy drinking but were able to communicate; 20 (31%) fulfilled neither criteria [56].
  Level 3

- A multivariate analysis reported that liver disease (OR 0.25; 95%CI 0.20 to 0.80; p=0.02) and postoperative status (OR 3.10; 95%CI 1.35 to 7.09; p=0.008) were associated with inappropriate placement on the CIWA-Ar protocol, with the former less likely and the latter more likely to experience inappropriate placement [56].
  Level 3

- There was no significant difference between those patients who received appropriate and those that received inappropriate therapy with respect the incidence of adverse events (not significant) [56].
  Level 3

2.6.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis related to the assessment and monitoring of patients with AAW was identified by the economic review.

The economic analysis developed for this guideline assessing the cost-effectiveness of the fixed-schedule dosing regimen of benzodiazepines or clomethiazole, compared to a

symptom-triggered dosing regimen, for the in-hospital management of patients with AAW, considered the use of a monitoring tool when managing patients using a symptom-triggered dosing regimen. The CIWA-Ar scale was used in the four clinical studies on which the economic analysis was based on (Daeppen 2002)[30], Saitz 1994[31], Lange-Asschenfeldt 2003[33], Weaver 2006[32]. In addition, the CIWA-Ar and the CIWA-AD scales are used in England and Wales where the symptom-triggered regimen forms part of the AAW management protocol, and experience from current practice was considered when developing the economic analysis. The full analysis is presented in Section A.4.

2.6.5 EVIDENCE TO RECOMMENDATIONS

The GDG noted that the majority of studies are representative of people admitted to general hospitals under the care of a number of different specialties rather than dedicated alcohol services.

The majority of studies involved a change in treatment regimen (for example, from fixed schedule to symptom-triggered dosing) whilst concurrently changing methods of assessment and monitoring. Education and training also form a component of a number of the studies. It is therefore impossible to identify the specific aspect of care that was associated with any change in patient outcomes.

It was noted that all of the protocol-based studies used an assessment scale to quantify and monitor symptoms of withdrawal. In some studies this was also used to guide pharmacological intervention. One prospective case series reported that the CIWA-Ar was valuable at identifying patients in early withdrawal who required drug therapy to avoid complications.

The GDG discussed the study which reported that a delay in assessment (greater than 24 hours) was associated with alcohol withdrawal complications. This reflects the group's experience that the late recognition of withdrawal leads to a more severe syndrome, and promotes the concept that alcohol misusers should be assessed as soon as possible after presentation for dependence (and therefore risk of withdrawal)(see 'Alcohol use disorders: diagnosis and clinical management of harmful drinking and alcohol dependence' [NICE clinical guideline in development]). Those patients in alcohol withdrawal should be assessed by an appropriately skilled health worker for the severity of AAW and the need for pharmacotherapy.

One study reported that some medical and surgical patients were inappropriately started on symptom-triggered dosing. This was deemed inappropriate if they were either unable to communicate or did not have a recent history of alcohol misuse, or both. Although this was not associated with adverse events, it further highlighted to the GDG the need for adequate training in those managing the syndrome. Some group members have had experience of symptom-triggered regimen being effective when in the hands of well-trained staff and ineffective when the staff are not appropriately trained.

One of the studies reported that changing from fixed to symptom-triggered regimen resulted in a decrease in the amount of medication prescribed and length of stay; compatible with recommendations made elsewhere in this guideline. A reduction in medication was reported in another study on patients with alcohol-related delirium admitted to the intensive care unit.

It was noted that none of the studies reported on patient experience.

2.6.6 RECOMMENDATIONS

R12 Assess people in acute alcohol withdrawal immediately on admission to hospital.

R13 Ensure that staff caring for people in acute alcohol withdrawal are trained in the assessment and monitoring of withdrawal symptoms and signs.

R14 Assess and monitor patients in acute alcohol withdrawal following locally specified protocols. Consider using a tool (such as the Clinical Institute Withdrawal Assessment – Alcohol, Revised [CIWA–Ar] scale) as an adjunct to clinical judgement.

2.7 WERNICKE'S ENCEPHALOPATHY

2.7.1 CLINICAL INTRODUCTION

The Wernicke-Korsakoff syndrome develops in problem drinkers who are thiamine deficient. However, other as yet unidentified factors must be important in its genesis as thiamine deficiency is not invariably associated with the development of this syndrome. ***Wernicke's encephalopathy*** comprises a triad of global confusion, eye signs and ataxia; the confusional state is accompanied by apathy, disorientation and disturbed memory, but drowsiness and stupor are uncommon. The ocular abnormalities include nystagmus, gaze palsies and ophthalmoplegia, while the ataxia affects the trunk and lower extremities. The clinical abnormalities may develop acutely or evolve over several days. The cerebral lesion is characterized by degenerative changes in the structures surrounding the third ventricle and aqueduct, particularly the mammilliary bodies. ***Korsakoff's psychosis*** is an amnesic state in which there is profound impairment of both retrograde and anterograde memory but relative preservation of other intellectual abilities; confabulation may be a feature. The cerebral lesion is characterized by changes in the dorsomedial thalamus. Korsakoff's psychosis generally develops after an acute episode of Wernicke's encephalopathy. However, some patients develop a combined syndrome, from the outset, with memory loss, eye signs and unsteadiness but without confusion; others do not develop either the eye signs or ataxia.

Post-mortem analysis has demonstrated that Wernicke's encephalopathy may occur in as many as 12.5% of chronic alcohol misusers [59],although Wernicke's encephalopathy or Korsakoff's psychosis (characterised by a chronic amnesic syndrome and short-term memory loss) has historically been diagnosed during life in only 5-20%[59-62]). The discrepancy between the pathological findings and the clinical recognition of the

syndrome may be explained by the fact that the classical presentation is seen in only 10% of patients [62].A presumptive diagnosis of the Wernicke-Korsakoff syndrome should therefore be made in patients with a history of alcohol misuse and one or more of the following otherwise unexplained symptoms: ataxia, ophthalmoplegia, nystagmus, confusion, memory disturbance, comatosed/unconscious, hypotension, and or hypothermia.

The pathogenesis is most likely linked to inadequate dietary intake and poor thiamine absorption. Oral thiamine absorption is limited by an active transport process, a single 10mg-30mg oral dose seeming to maximise absorption. No additional benefit is apparent from higher oral doses as passive diffusion does not occur[63]. Absorption of thiamine appears to be independently affected by both alcohol and malnutrition. Absorption is reduced by around 70% in abstinent malnourished previous alcohol misusers and the remaining absorption is reduced by a further 50% in a third of patients by the concomitant administration of alcohol[63] . Other factors commonly seen in alcohol misusers such as poor diet, diarrhoea and vomiting may additionally affect absorption[64,65]. Once alcohol is stopped, oral thiamine absorption may take six weeks to return to normal[64].

It is now common practice to give patients with Wernicke's encephalopathy (and those with a presumptive diagnosis) intravenous thiamine but the dose and length of treatment required is unclear. It is also common practice to give prophylactic thiamine to hospitalised malnourished harmful drinkers but there are no routinely used evidence-based recommendations for the route of administration, dose and length of treatment. It is also not clear which patients are most at risk of Wernicke's encephalopathy and which require long term prophylaxis or the dose or form that this prophylaxis should take.

The GDG searched the literature around the following clinical questions:

a)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*

b) Which patients are at risk of developing Wernicke's encephalopathy and therefore require prophylactic treatment?

2.7.2 CLINICAL METHODOLOGICAL INTRODUCTION

Studies were included that reported on the safety, efficacy, dosing or treatment duration of Pabrinex, oral b vitamin, oral thiamine, multivitamins, placebo or any combinations or comparison of these for the prevention and/or treatment of Wernicke's encephalopathy. Outcomes included mortality and morbidity.

Studies comparing the safety and efficacy of intravenous (i.v.) or intramuscular (i.m.) thiamine or multivitamins compared with oral preparations reporting on tissue thiamine levels as an outcome were also included.

Five studies were included in the review[66-70].

One randomised-control trial reported on the use of thiamine in the prevention of Wernicke's encephalopathy [68]. See Table 2-14below for study details.
Level 1+

Table 2-14. Summary of included study details.

	Population	Intervention	Outcome	Follow up
AMBROSE 2001[68] N=107 **Level 1+**	All patients conformed to a DSM-IV diagnosis of alcohol dependence but did not have the triad of acute symptoms of Wernicke-Korsakoff syndrome (WKS)	Randomly assigned to 1 of 5 treatments: 1. **5 mg of thiamine hydrochloride** im 1/day for 2 days n=20 2. **20 mg of thiamine hydrochloride** im 1/day for 2 days n=24 3. **50 mg of thiamine hydrochloride** im 1/day for 2 days n=21 4. **100 mg of thiamine hydrochloride** im 1/day for 2 days n=24 5. **200 mg of thiamine hydrochloride** im 1/day for 2 days n=18	Test of working memory (delayed alternation task) - assessed by psychologist blind to treatment groups.	3 days

Two case series reported on the use of thiamine for the treatment of Wernicke's encephalopathy [66,67]. These two studies used the same cohort of patients, with the more recent publication reporting on different outcomes. See **Table 2-15**below for study details.
Level 3

Table 2-15. Summary of study details.

	Population	Intervention	Outcome	Follow up
WOOD 1986/1995[66,67]	Patients admitted over a 33 month period with a diagnosis of acute Wernicke's	Thiamin hydrochloride - administered after	Thiamine status, gross nutritional state, biochemical response to	6-18 months

N=32 **Level 3**	encephalopathy (WE). A diagnosis of WE was recorded if ophthalmoplegia was present with at least 2 of 3 other features- nystagmus, ataxia and global confusional state.	initial examination - first dose intravenous - then given intramuscularly for 1 week - all other vitamins were withheld for 1 week - after 1 week, patients received thiamine and multi-vitamin by mouth	treatment, Korsakoff's psychosis, clinical features.		

One RCT compared treatment with thiamine i.m. with oral thiamine and a control group on no vitamins [70]. See Table 2-16 below for study details.
Level 1+

One non-randomized trial [69] compared treatment with i.v. thiamine with oral thiamine and a control group given placebo [69]. See Table 2-16 below for study details.
Level 2+

Table 2-16. Summary of study details.

	Population	Intervention	Comparison	Outcomes	Follow up
BAINES 1988[70] **Level 1+** N=25	Patients admitted to a special unit for treatment of alcohol dependence, drinking up to the day of admission but not requiring urgent medical treatment and showing the capacity for rehabilitation.	Multivitamin supplementation containing 250mg thiamine by single i.m. injection for 5 days N=8	1) Oral multivitamin supplementation containing 50mg thiamin 5 times daily for 5 days N=8 2) control group who received no vitamins N=9	Erythrocyte thiamine diphosphate (TDP) (measure of the physiologically active form of thiamine in tissue)	7 days
BROWN	Patients admitted to the detoxification unit	Group A: Parentrovite i.v. HP 10ml daily	Group B: oral orovite 1 tablet 3 times a day for 5	Thiamine, riboflavin, pyridoxine status	5 days

1983[69] **Level 2+** N=97	who had not taken vitamin preparations within one month of admission and who had no signs of Wernicke's encephalopathy. All patients had been drinking in excess of 150cl of alcohol per day and were chemically dependent.	for 5 days (1 dose of parentrovite contains 250mg thiamine HCl) N=26 By day 5 they had received 1250 ml i.v. thiamine.	days. (3 tablets of orovite contains 150mg thiamine) By day 5 they had received 750mg of oral thiamine and 100mg i.v N=24 Group C: placebo given 3 times per day for 5 days. N=23	(via erythrocyte transketolase (ETK), glutathione reductase (EGR) and glutamate-oxaloacetate transaminase (EGOT)	

One case-control study was excluded due to low quality methodology with no statistical analysis of results, no consideration of potential confounders and no clear differentiation made between cases and controls. [71].

Level 2-

No studies were found that directly answered the question 'Which patients are at risk of developing Wernicke's encephalopathy and therefore require prophylactic treatment?'

2.7.3 CLINICAL EVIDENCE STATEMENTS

►Prevention of Wernicke's encephalopathy

Test of working memory (delayed alternation task):

- There was a significant difference between dosage groups in the number of trials taken to reach the alternation task criterion, p=0.047, with 50 mg thiamine treatment group needing the fewest trials (38) to reach the criterion and the 20mg treatment group needing the most (56).
- Although the 50mg treatment group appeared to require fewer trials, post-hoc comparisons made between the 50mg group and the other treatment groups were non-significant (5 versus 50 mg p=0.166; 20 versus 50mg p=0.043; 100 versus 50mg p=0.090; 200 versus 50mg p=0.561; critical alpha for all comparisons 0.013)
- A comparison between the 200mg treatment group and the mean of the other dosage groups was significant, p=0.031 } [68]

►Treatment of Wernicke's encephalopathy

The initial study by Wood et al.[66] reported on change in clinical characteristics between admission and follow-up after treatment with thiamine hydrochloride. See Table 2-8 and Table 2-9 below.

Level 3

Table 2-17.

On admission and discharge (N=32)				
Outcome	**On admission**	**At discharge**	**RR (95% CI)**	**P value**
Ophthalmoplegia	30/32 (94%)	2/32 (13%)	15.00 (3.91, 57.57)	<0.001
Nystagmus	29/32 (91%)	26/32 (81%)	1.12 (0.91, 1.36)	0.29
Long-term memory deficit	28/31 (90%)	18/31 (58%)	1.56 (1.13, 2.14)	<0.01
Short-term memory deficit	30/30 (100%)	24/29 (83%)	1.20 (1.01, 1.44)	<0.05
Peripheral neuropathy:				
Muscle weakness	16/31 (51%)	6/30 (20%)	2.58 (1.17, 5.70)	<0.05
Reflex impairment	30/32 (94%)	27/30 (90%)	1.04 (0.90, 1.21)	0.59
Sensory impairment	22/31 (71%)	17/30 (57%)	1.25 (0.85, 1.84)	0.25

Table 2-18.

At discharge and at last visit (N=27)				
Outcome	**At discharge**	**At last visit**	**RR (95% CI)**	**P value**
Ophthalmoplegia	4/22 (15%)	2/27 (15%)	2.45 (0.49, 12.17)	0.27
Nystagmus	22/27 (82%)	21/27 (78%)	1.05 (0.80, 1.37)	0.74
Long-term memory deficit	14/26 (54%)	21/26 (81%)	0.67 (0.45, 1.00)	0.05
Short-term memory deficit	17/24 (71%)	24/26 (92%)	0.77 (0.58, 1.01)	0.06
Peripheral neuropathy:				
Muscle weakness	5/25 (20%)	3/24 (13%)	1.60 (0.43, 5.97)	0.48
Reflex impairment	23/25 (92%)	21/25 (92%)	1.10 (0.89, 1.35)	0.39

Sensory impairment	12/25 (48%)	10/25 (40%)	1.20 (0.64, 2.25)	0.57
Korsakoff's psychosis	14/27 (52%)	16/26 (52%)	0.84 (0.52, 1.35)	0.48

A significant reduction was seen in:

- Ophthalmoplegia
- Long-term memory deficit
- Short-term memory deficit
- Muscle weakness[66].

Level 3

►Mortality

- At long term follow up (5 lost) 2/27 (7%) patients died and three others could not be located.[66].

Level 3

The second publication from the same cohort of patients reported further details on ophthalmoplegia, nystagmus, global confusion state and global severity of Wernicke's encephalopathy, see below [67].

Level 3

►Ophthalmoplegia

- The participants of improvement was affected by the severity of liver disease, $p<0.001$ and by the severity of fatty liver, $p<0.001$
- Participants with no fatty liver had the fastest improvement in ophthalmoplegia to treatment, but all participants reached the same level by the end of 14 days. [67]

Level 3

►Nystagmus

- Scores for individual tests of nystagmus all showed improvement, $p<0.01$
  At discharge only six participants were completely free of nystagmus[67].

Level 3

►Global confusion state (see Table 2-11 below)

- The state of consciousness rapidly improved within hours of thiamine treatment, $p<0.001$ and continued to improve slowly, $p<0.02$
- The severity of disorientation in time improved over time, $p<0.001$, but improvement slowed by 7 days, $p<0.05$, and thereafter, $p<0.01$.
- By discharge, most participants were still disorientated in time and 18 patients still did not know the day of the week[67].

Level 3

Table 2-19.

Global severity of acute Wernicke's	Admission	Discharge
Class 4: ophthalmoplegia, ataxia +/- confusion	3/32	0/32
Class 3: ophthalmoplegia, nystagmus, ataxia +/- confusion	27/32	4/32 (a)
Class 2: nystagmus, ataxia +/- confusion	2/32 (b)	22/32
Class 1: nystagmus, +/- confusion	0/32	0/32
Class 0: complete absence of these features	0/32	6/32

(a)- Residual ophthamoplegia only

(b)- One case was subsequently found to have received thiamine just prior to assessment.

Limitations:

- The study did not report the dose of thiamine given. It is also possible that the dose of thiamine that they gave was too small and/or the treatment period too short.

► **Parenteral versus oral thiamine**

The response of Erythrocyte thiamine diphosphate (TDP) level

One study reported on the response of erythrocyte TDP level when giving oral compared to i.m. (parental) preparations of thiamine [70]. See Table 2-11 below for results.

Level 1+

Table 2-20. (Normal reference range for TDP level 165-286 nmol/l)

The response of erythrocyte thiamine diphosphate (TDP) level					
	None (n=9)	**Oral (n=8)**	**Parenteral (n=8)**	**RR (95% CI)**	**P value**
	Mean (± S.D.) Erythrocyte TDP (nmol/l)				
Day 0 (pre-treatment)	218 (± 29)	218 (± 27)	207 (± 47)	Oral versus none: 0.00 (-26.63, 26.63)	Oral versus none: 1.00
				Parenteral versus none: -11.00 (-48.68, 26.68)	Parenteral versus none: 0.57
Day 1 (post 250mg thiamine orally or parenterally)	209 (± 39)	265 (± 51)	328 (± 117)	Oral versus none: 56.00 (12.43, 99.57)	Oral versus none: 0.01
				Parenteral versus none: 119.00 (61.12, 176.88)	Parenteral versus none: <0.001
Day 7 (post 5 × 250mg thiamine as above)	220 (± 56)	308 (± 64)	298 (± 75)	Oral versus none: 88.00 (30.51, 145.49)	Oral versus none: 0.003
				Parenteral versus none: 78.00 (14.44, 141.56)	Parenteral versus none: 0.02
Change in mean after 250mg thiamin, or control	-9	+47	+121	-	-
Change in mean after 5 × 250mg	+2	+90	+91	-	-

thiamine or control					

Limitations:

- There is some debate over the most accurate measure of tissue thiamine level, with previous studies reporting erythrocyte enzyme transketolase (ETKA) rather than TDP. This may affect the final results.
- This study excluded patients with vitamin deficiencies, which may be an important group of patients in which thiamine is used. Also there was no explanation of what defined a patient as vitamin deficient..
- Short-term follow up of only 7 days may have not been a sufficient time to see results.

►Response of erythrocyte transketolase (ETK) activity

One study reported on the response of ETK to treatment with intravenous and oral thiamine compared with placebo [69].

- **intravenous thiamine (n=26) versus placebo (n=23) at day 2:**
  - Mean ± SD: 68.7*± 14.0 versus 68.4 ± 13.8; MD 0.30 (-7.50, 8.10), p=0.94
- **intravenous thiamine (n=26) versus placebo (n=23) at day 5:**
  - Mean ± SD: 75.5**±12.9 versus 75.8**± 15.2; MD -0.30 (-8.25, 7.65), p=0.94
- **Oral thiamine (n=24) versus placebo (n=23) at day 2:**
  - Mean ± SD: 70.0* ±12.5 versus 68.4 ± 13.8; MD 1.60 (-5.94, 9.14), p=0.68
- **Oral thiamine (n=24) versus placebo (n=23) at day 5:**
  - Mean ± SD: 76.8**± 11.4 versus 75.8**± 15.2; MD 1.00 (-6.71, 8.71), p=0.80[69]

Level 2+

Note: the significant differences (within each group) from the previous mean are indicated at the 95% (*) and 99.9% (**) confidence levels.

Response of ETK activity to vitamin supplementation in patients originally deficient

- **intravenous thiamine (n=16) versus placebo (n=15) at day 2:**
  - Mean ± SD: 59.5* ± 7.8 versus 60.6 ± 9.9; MD -1.10 (-7.40, 5.20), p=0.73
- **intravenous thiamine (n=16) versus placebo (n=15) at day 5:**
  - Mean ± SD: 66.8**± 6.1 versus 67.9** ± 12.1 ; MD -1.10 (-7.91, 5.71), p=0.75
- **Oral thiamine (n=16) versus placebo (n=15) at day 2:**
  - Mean ± SD: 64.4* ± 8.5 versus 60.6 ± 9.9 ; MD 3.80 (-2.72, 10.32), p=0.25
- **Oral thiamine (n=16) versus placebo (n=15) at day 5:**
  - Mean ± SD: 71.8** ± 8.2 versus 67.9** ± 12.1 ; MD 3.90 (-3.42, 11.22), p=0.30[69]

Level 2+

Note: the significant differences (within each group) from the previous mean are indicated at the 95% (*) and 99.9% (**) confidence levels.

Limitations:

- The measure ETK may not be the most accurate measure of tissue thiamine levels.
- The doses of oral and parenteral thiamine given were not equal, and may not have been given at an adequate dose.
- Both groups were given i.v. thiamine at the start, which may have affected the final results.
- Short term follow up of only five days may not have been sufficient.

2.7.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis was identified assessing the cost-effectiveness of vitamin supplementation for the treatment/prevention of Wernicke's encephalopathy. Costs and resource use information associated with the use of vitamin supplementation for the treatment/prevention of Wernicke's encephalopathy were presented to the GDG.

2.7.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Vitamin-supplementation options used for the treatment/prevention of Wernicke's encephalopathy have a low-drug cost (especially oral preparations). Pabrinex is the only treatment given parenterally for rapid correction of acute vitamin depletion and is more costly than oral preparations (few pence for high dose of oral preparations versus £1.96 for Pabrinex intravenous preparation [10 ml in 2 ampoules] and for Pabrinex intramuscular preparation [7 ml in 2 ampoules][28,43]. Parenteral treatment is normally given to patients when hospitalized for a co-morbidity and therefore use of Pabrinex does not affect the length of hospital stay in its current use.

The use of parenteral thiamine (Pabrinex) is associated with a potentially serious allergic adverse reaction that may rarely occur during, or shortly after administration. This reaction may incur extra treatment costs in addition to morbidity. Additional staff time is also associated with giving parenteral preparations.

The BNF No. 56[43] recommends that the potential serious allergic adverse reaction should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential, and that facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

2.7.6 EVIDENCE TO RECOMMENDATIONS

The GDG noted that the absence of RCTs on this subject would mean any recommendations would need to be by consensus. Due to this lack of RCTs and the

potentially catastrophic long term effects of acute thiamine deficiency some of the evidence that was presented was based on clinical studies of thiamine absorption and metabolism.

The GDG first considered evidence on prevention of Wernicke's encephalopathy with thiamine prophylaxis. It then considered treatment where there was a presumptive or actual diagnosis.

Prophylaxis

In order to determine which patients should receive prophylaxis and how, the risk factors for thiamine deficiency and the absorption of oral thiamine were discussed. Malnourishment is a key pre-disposing factor to thiamine deficiency and the risk factors for malnourishment are dietary intake reduction, nausea and vomiting. Alcohol intake and liver dysfunction also predispose to thiamine deficiency. It was emphasised that patients who are malnourished are not only more likely to be thiamine deficient, but also likely to have impaired absorption of oral thiamine.

When deciding which patients should receive prophylaxis certain other factors were felt to be important. These were; compliance, the treatment for the underlying malnutrition, cost and the inconvenience of daily tablets or parenteral thiamine. We divided patients into low and high risk of developing Werniecke's encephalopathy.

► 'Low risk' group

This was defined as people who are alcohol-dependent but otherwise eating a normal diet and with no other alcohol-related problem. This will tend to be people with mild or moderate dependence as those with more severe dependence will start to neglect their diet. It was not felt that there was evidence to recommend thiamine to this group. The sub-group of younger people was discussed because nutritional requirements are higher and they may be more susceptible to alcohol-induced neuro-degeneration. It was decided not to make a separate recommendation about thiamine use in this group because of a lack of evidence.

In conclusion, the GDG noted that it could not recommend widespread use of thiamine in this low risk group.

► 'High risk' group

The GDG discussed features that might necessitate thiamine use in hazardous, harmful or dependent drinkers to prevent Wernicke's. The GDG highlighted the following:

- Alcohol-related liver disease
- medically-assisted withdrawal from alcohol (planned or unplanned)
- acute alcohol withdrawal
- malnourishment or risk of malnourishment; this may include;
    - weight loss in past year
    - reduced BMI
    - loss of appetite
    - nausea and vomiting

    - a general impression of malnourishment
- homelessness
- hospitalised for acute illness
- hospitalised for co-morbidity or another alcohol issue.

The GDG decided that any of these risk factors were enough to recommend prophylactic thiamine. It was recognised that an adequate diet would likely suffice, but it was felt that additional prophylaxis should be provided in some cases. Although absorption is inhibited in some of these situations, it was felt that oral thiamine would usually be adequate prophylaxis.

Concerns were raised about patients with severe withdrawal or with co-morbid conditions that may mask the neurological signs of Wernicke's such as encephalopathy. These concerns arise from evidence showing that some patients develop Wernicke's during withdrawal of alcohol. It was felt that parenteral therapy should be used if withdrawal is severe enough to warrant hospital attendance or admission. It was also emphasised that patients with comorbid conditions that may mask the features of Wernicke's should be managed cautiously. The index of suspicion for considering Wernicke's in these patients should be high and the threshold for considering following the treatment recommendations should be low.

Diagnosis and treatment

The GDG discussed the issue of treatment of Wernicke's encephalopathy. The main themes of the discussion were the difficulty in making the diagnosis and the catastrophic nature of a missed diagnosis. Most patients do not present with the classical triad of symptoms so there needs to be a high index of clinical suspicion. The GDG discussed the difficulty in making a diagnosis in the confused patient who abuses alcohol and emphasised the importance of confusion in a patient with a blood alcohol concentration of zero.

Due to the need for rapid absorption of thiamine in patients at high risk of developing Wernicke's encephalopathy the oral route of administration was felt to be inadequate. It was noted that blood thiamine levels fall rapidly after administration so the treatment should be given more than once a day. Due to the concern of long term brain injury, it was felt that patients with even a low index of suspicion for Wernicke's encephalopathy should be treated with parenteral thiamine. With no evidence to guide the period of treatment, the recommendation was based on the group's expert consensus.

2.7.7 RECOMMENDATIONS

R15 Offer prophylactic oral thiamine to harmful drinkers in any of the following situations:

- if they are malnourished or at risk of malnourishment
- if they have decompensated liver disease
- if they are in acute withdrawal

- before and during a planned detoxification.

R16 Give prophylactic parenteral thiamine to harmful or dependent drinkers if they are malnourished or at risk of malnourishment and attend an emergency department or are admitted to hospital with an acute illness.

R17 Give parenteral thiamine to people with suspected Wernicke's encephalopathy. Treatment should continue for 5 days unless the person recovers or an alternative diagnosis is made.

2.7.8 Research Recommendations

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

3 ALCOHOL-RELATED LIVER DISEASE

Alcohol produces a spectrum of liver injury but only a minority of individuals misusing alcohol, some 20 to 30%, develop cirrhosis; of these, approximately 15% will develop hepatocellular carcinoma as a terminal event. The factors that determine an individual's susceptibility to develop significant alcohol-related liver injury are largely unknown.

The majority of individuals abusing alcohol will develop fatty change in their liver. This lesion is not in itself harmful and quickly reverses when alcohol is withdrawn. Individuals are usually asymptomatic and generally present incidentally.

Individuals who develop alcohol-related hepatitis may remain asymptomatic and not be detected until they present for other reasons. Alternatively they may present with clear evidence of chronic liver disease such as jaundice, hepatomegaly and fluid retention.

The outcome in individuals with alcohol-related hepatitis is determined by their subsequent drinking behaviour, their gender and by the severity of the disease. The mortality rate in individuals presenting with severe hepatitis may be as high as 40%.

Individuals who develop alcohol-related cirrhosis may remain asymptomatic and come to attention only if inadvertently identified, for example, at an insurance medical examination. Alternatively, they may present with features of hepatocellular failure and portal hypertension, such as jaundice, fluid retention, blood clotting abnormalities, hepatic encephalopathy and variceal haemorrhage.

The outcome for patients with cirrhosis is determined largely by the degree of decompensation at presentation and by the subsequent drinking behaviour. The presence of superimposed alcohol-related hepatitis and the development of hepatocellular carcinoma significantly reduce survival.

The most important management aim is to ensure long-term abstinence from alcohol. Complications such as fluid retention and variceal bleeding have specific therapies. This chapter will review the role of liver biopsy in the investigation of alcohol-related liver disease and the management of alcohol-related hepatitis. The GDG will also consider referral for orthotopic liver transplantation for the treatment of patients with decompensated alcohol-related cirrhosis.

3.1 ROLE OF THE LIVER BIOPSY

3.1.1 CLINICAL INTRODUCTION

Although the first diagnostic liver biopsy was reported in 1923 [72], the procedure has only been used regularly in the last 50 years or so. During this time, a variety of techniques have been used, and the indications have changed as non-invasive diagnostic tests have been introduced.

Liver biopsy can be performed percutaneously, transvenously (with the transjugular approach being the most common) or, rarely, laparoscopically. Of these three techniques, the first two are the ones most commonly performed in patients suspected of having alcohol-related liver injury. Percutaneous liver biopsies themselves can be transthoracic or subcostal and either ultrasound guided or 'blind'. The transjugular approach is reserved for patients with contra-indications to the percutaneous approach such as ascites or coagulation defects. Unfortunately, these contra-indications are quite common in liver disease, particularly in patients with alcohol-related hepatitis.

The purpose of liver biopsy in alcohol-related liver disease (ALD) is to confirm the diagnosis and stage the disease. Staging is a practice common to all types of liver disease and involves a pathological semi-quantification of the degree of fibrosis or liver scarring. This is absent in a healthy liver and advanced in the case of cirrhosis. With the advent of serum and radiological markers of fibrosis, there is much debate about the role of liver biopsy for this purpose. If non-invasive markers are validated against the histological 'gold standard', they make an attractive alternative to an invasive procedure. This debate is one which covers all of hepatology and is not specific to alcohol-related liver disease. As such, the GDG did not include a clinical question around the role of liver biopsy in the staging of alcohol related liver injury. The clinical questions the GDG asked relate to the issue of whether a liver biopsy is required to confirm the diagnosis of ALD or to determine whether there is an active alcohol-related hepatitis.

The diagnosis of alcohol-related liver disease is based on the history (a confirmed history of alcohol misuse and the absence of other risk factors for liver disease) and examination and certain abnormalities of laboratory variables. Radiology, particularly ultrasound, can also help with the diagnosis. It is important to exclude other liver diseases which could cause the laboratory abnormalities.

In cases where there are laboratory abnormalities and no clear alcohol history or a high index of suspicion of another liver condition there may well be an increased incentive to biopsy. The question is, if one suspects that a patient has alcohol-related liver disease and the clinical work-up has excluded other causes of liver disease, is a biopsy required to confirm the clinical suspicion?

The first clinical question therefore asked and upon which the literature was searched is:

> *'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?'*

Alcohol-related hepatitis (alcoholic hepatitis or AH) is an inflammatory condition of the liver and part of the spectrum of ALD. It is a histological diagnosis with the characteristic features of neutrophil infiltration, hepatocyte ballooning and Mallory bodies. It may arise *de novo* or superimposed on an already established cirrhosis.

Alcohol-related hepatitis may remain silent and its presence may not be marked by any untoward clinical symptoms or signs. However, severe hepatitis presents with the features of hepatic decompensation which include jaundice, gastro-intestinal bleeding, coagulopathy and encephalopathy. The prognosis can be determined using a variety of clinical scores, with the most widely used being Maddrey's discriminant function (DF), a score based on the bilirubin and prothrombin time. As well as being a useful prognostic marker, this score has also been used to determine which patients will benefit most from specific therapies for AH.

The problem with making clinical decisions based on the prothrombin time and bilirubin level is that these can be abnormal in ALD in patients who do not have AH. This can happen in advanced cirrhosis without superimposed AH, particularly if there is decompensation for another reason such as gastrointestinal bleeding or infection.

Some clinicians will insist upon a liver biopsy before providing specific therapies for severe AH. Others will argue that an experienced clinician will be able to make the diagnosis of AH without biopsy. Again the answer will depend on how frequently the pre-biopsy diagnosis of AH is proven to be incorrect when histology is obtained.

The second clinical question therefore asked and upon which the literature was searched is:

> *'What is the safety and accuracy of laboratory and clinical markers versus liver biopsy for the diagnosis of alcohol related hepatitis versus decompensated cirrhosis?'*

3.1.2 CLINICAL METHODOLOGICAL INTRODUCTION

Accuracy of liver biopsy

Studies were included that reported on the accuracy of a clinical judgement based on history, clinical examination and routine laboratory and/or ultrasonography findings or routine laboratory findings. Papers were excluded if they reported on the diagnostic accuracy of individual laboratory findings or whether individual laboratory findings differentiated between clinical conditions.

Nine studies were included in the evidence review [73,74] [75] [76] [77] [78] [79] [80] [81].

Level 2+

The details of these studies are summarised in Table 3-1 below. The studies varied considerably with respect to what aspects of clinical management, laboratory findings etc they reported.

Table 3-1. Summary of included studies.

Study, number of biopsies	Rationale	Prebiopsy diagnosis	Final diagnosis (alcohol-related only)	Patient Population	Comparison
Alcoholic liver disease					
ELPHICK 2007[73] **Level 1b++** N=110	Reported on the histological features suggestive of ALD in patients with presumed decompensated ALD	110/110 (100%) decompensated ALD	104/110 (95%) decompensated ALD 78/110 (71%) had cirrhosis	Patients with presumed decompensated ALD defined as Child's Grade B or C, consumption of at least 60 units of alcohol per week (men) or 40 units/week (females) for at least 5 yrs prior to the episode of decompensation, no other liver disease on extensive noninvasive workup	Histological features of ALD: fatty infiltration, a neutrophil infiltrate, ballooning hepatocyte degeneration, and Mallory's hyaline
VAN NESS 1989[78] **Level 1b+** N=90	Reported on the diagnostic accuracy of diagnosis made before biopsy on the basis of non-invasive work-up (history, physical examination, laboratory values and imaging) and a final diagnosis made after biopsy for alcoholic liver	26/90 (29%) ALD: alcoholic steatosis 2/26 (8%), 12/26 (46%) mild alcoholic liver disease, 2/26 (8%) moderate alcoholic liver disease, 10/26 (38%) alcoholic cirrhosis 19/90 fatty liver, 25/90 chronic necroinflammatory disease, 20/90 Misc	23/90 (26%) alcoholic liver disease: 7/23 alcoholic cirrhosis, 5/23 alcoholic hepatitis with fibrosis, 4/23 alcoholic hepatitis without firbrosis, alcoholic foamy degeneration 2/23, alcoholic siderosis 1/23	Patients with elevated liver associated enzymes. Patients with previously undiagnosed liver disease were included if at least one liver-associated enzyme (asparate aminotransferase (AST), alkaline phosphatase (AP), alanine	Pre-biopsy (clinical diagnosis The complete blood count, platelet count, prothrombin time and partial thromboplastine time were measured within 3 days before the biopsy

	disease			aminotranferase (ALT), gamma glutamyl transpeptidase (GGT)) was elevated to 1.5 times the upper limit of normal for 3 months or more	
TALLEY 1988[77] **Level 1b+** N=108	Clinical diagnosis recorded before biopsy was compared with the histological diagnosis of an experienced histopathologist.	35/108 (32%) ALD 73/108 (78%) non-ALD	25/108 (23%) alcoholic liver disease: 25/35 (71%) with a prebiopsy diagnosis had a final diagnosis of ALD: cirrhosis 14/25 (56%), cirrhosis and alcoholic hepatitis 1/25 (4%), alcoholic hepatitis 6/25 (24%), 1/25 (4%) fibrosis and lipogranulomas	All patients who underwent liver biopsy regardless of their alcohol intake. All patients had prebiopsy diagnosis of hepatic disease and undergoing biopsy for the first time. Of these, 35/108 (32%) had a prebiopsy diagnosis of ALD and 73/108 (68%) non-ALD	Clinical diagnosis Included: Bilirubin, alanine aminotransferase (ALT), aspirate aminotransferase (AST), gamma glutamyltransferase (GGT), serum alkaline phosphatise, albumin
Alcoholic hepatitis/cirrhosis					
KRYGER 1983[76] **Level 1b++** N=357	Patients who had undergone liver biopsy. Clinicians reviewed the case histories without knowledge of the biopsy results.	200/357 (56%) had a history of alcoholism	172/357 (48%) alcohol-induced changes: 80/357 (22%) alcoholic cirrhosis, 84/357 (26%) steatosis, 8/357 (2%) alcoholic hepatitis without	Patients who had undergone liver biopsy	Anamnestic, clinical and biochemical findings

			cirrhosis		
THABUT 2006[74] **Level 1b++** N=225	Diagnostic accuracy of a panel of biomarkers (AshTest) for the diagnosis of alcoholic hepatitis in patients with alcoholic liver disease. The results were compared with those obtained from using Maddrey discriminant function ≥ 32 and the AST:ALT ratio	**Diagnosis based on biopsy** **Cirrhosis:** Training group 57/70 (81%) Validation group 1: 56/62 (90%) Validation group 2: 23/93 (25%) **Alcoholic hepatitis features:** **Necrosis and polynuclear neutrophils:** Training group 42/70 (60%) Validation group 1 12/62 (19%) Validation group 2 22/93 (24%) **At least one hepatitis feature:** Training group 61/70 (87%) Validation group 1 32/62 (52%) Validation group 2 65/93 (70%)		Patients with an alcohol intake >50 g/d with available serum and liver biopsy	AshTest: AST, total bilirubin, GGT, macroglobulin, Apo A1, haptoglobin
VANBIERVLIET 2006[75] **Level 1b++** N=104	Reported on the diagnostic accuracy of CRP for alcoholic hepatitis in heavy drinkers	55/101 (55%) mild fibrosis, 46/101 (45%) significant liver fibrosis	20/104 (19.8%) cirrhosis 29/104 (30%) acute alcoholic	Patients admitted to a liver unit for detoxification and evaluation	C-Reactive Protein (CRP)

			hepatitis		
GOLDBERG 1986[79] **Level 1b+** N=89	Patients with clinically mild biopsy-proven alcoholic hepatitis were followed-up for ≥ 30 months. The diagnostic accuracy of laboratory tests for cirrhosis was reported	89/89 (100%) mild biopsy-proven alcoholic hepatitis	34/89 (38%) cirrhosis	Patients with biopsy-proven alcoholic hepatitis and 'seemingly' mild (bilirubin ≤ 5 mg/dl) liver disease. An alcoholic was defined as a history of consuming more than 80 g/day of ethanol during the preceding year. Any alcoholic with a history of recent drug abuse or the presence of HBsAg was excluded	The step-wise logistic discriminant analysis identified IgA, prothrombin time and SGOT/SGPT ratio (in order of importance) as the best predictors of cirrhosis Final model of discriminate function (DF) was derived to predict the probability of being cirrhotic, where DF = 0.606 (SGOT/SGPT) + 9.43 (IgA), with IgA expressed as g/dl
KITADAI 1985[81] **Level 1b+** N=67	Diagnostic accuracy of age, total alcohol intake, hepatomegaly and 12 liver function tests for biopsy-proven alcoholic liver cirrhosis and hepatitis	Diagnosis based on biopsy: 37/67 (55%) alcoholic liver cirrhosis, 14/67 (24%) alcoholic hepatitis, 7/67 (9%)		Patients classified at habitual drinkers with liver injury; all presented history of daily alcohol consumption of more than 90 ml ethanol equivalents per day for over 5 yrs	Age, total alcohol intake, hepatomegaly and 12 liver function tests
IRELAND 1991[80] **Level 2+** N=117	Review of patients with suspected alcoholic liver disease who had undergone	Raised GGT 17/117 (15%) Raised AST and GGT 34/117	17 /117 (14.5%) cirrhosis 18/117 (15%) hepatitis	Patients with suspected alcoholic liver disease	Raised GGT Raised AST and GGT

	biopsy. Patients were grouped into those with raised GGT, raised GGT, increased AST activity with or without raised GGT or widespread abnormal liver function tests	(29%) Widespread abnormal results 66/117 (56%)			Widespread abnormal results

Seven studies stated that the biopsy was performed blind to the pre-biopsy diagnosis [73 74 75 76 77 78 79]. One study did not state if the biopsy diagnosis was performed blind [80]. One study involved re-classifying data using a decision making model and therefore can be considered 'blind' [81].

Level 2+

It should be noted that the studies may be vulnerable to selection bias, due to the necessary inclusion criteria of liver biopsy. Patients with ALD who undergo biopsy are more likely to have severe disease or more than one medical condition than those who do not undergo biopsy. For example, 113/355 (32%) of patients with presumed decompensated ALD attending a liver unit had liver histology and were therefore eligible for inclusion [73].

Level 1b

One study involved histological diagnosis based on needle biopsy in the majority of patients (101/110, 92%) but also postmortem specimens (7/110, 6%) or explants at liver transplantation (2/110, 2%). 13/110 (12%) tissue specimens were performed prior to their first episode of decompensation ALD (median 5.4 years) and 41/110 (37%) were obtained after the date of first presentation with decompensation (usually to establish alcoholic hepatitis for patients who may require corticosteroid therapy). 56/110 (51%) specimens were obtained more than 31 days (median 15.6 months) after first presentation with decompensation [73].

Level 1b

Safety of liver biopsy

For this question 15 papers were identified that reported on the safety of liver biopsy, reporting on the agreed outcomes, namely death, bleeding, perforation and infection. The populations studied included patients with all forms of liver disease (not just alcohol related liver disease).

Some studies were included if they compared outcomes for different needle types, or for inpatient versus outpatient liver biopsy. For percutaneous liver biopsy, studies were excluded if the number of biopsies was less than 500 and for transjugular/ transvenous less than 100. The large amount of evidence in this area led to this restricted inclusion criteria in order to produce a manageable and meaningful review.

The studies were reported according to the type of biopsy performed:

- Percutaneous
- Transjugular/ transvenous biopsy

►***Percutaneous biopsy***

Twelve studies reported on the safety of percutaneous liver biopsy.[82-93]

►***Transjugular/ transvenous biopsy***

Three studies reported on the safety of transjugular/transvenous liver biopsy.[94-96]

3.1.3 CLINICAL EVIDENCE STATEMENTS

Accuracy of liver biopsy

►***Alcoholic liver disease***

In a review of 'heavy' drinkers with decompensated liver disease with a presumed diagnosis of ALD (based on alcohol history and extensive non-invasive workup), a total of 104 of the 110 (95%) patients had at least one of the histological features suggestive of ALD: fat, Mallory's hyalin, neutrophilic infiltrate, and hepatocyte ballooning. These features were more prevalent in tissue obtained within a month after presentation with decompensation than in that obtained before decompensation or more than one month after. In patients with presumed decompensated ALD, other liver diseases are uncommon [73].

Level 1b

The diagnosis of patients with chronically elevated liver enzymes (N=90) on the basis of history, physical examination, laboratory findings and imaging studies was compared with that based on histology. The results are presented in Table 3-2 below [78].

Table 3-2. Summary of results.

	Final diagnostic group			
	Alcohol (N=23)	Fatty liver (N=27)	Chronic necroinflammatory disease (N=26)	Misc (N=24)
Positive predictive value	88 (95%CI 75 to 100)	56 (37 to 75)	81 (66 to 96)	65 (46 to 84)
Negative predictive	97 (90 to 100)	90 (79 to 100)	92 (82 to 100)	87 (75 to 100)

value				
Sensitivity	91 (79 to 100)	59 (40 to 78)	81 (66 to 96)	63 (44 to 82)
Specificity	96 (88 to 100)	89 (77 to 100)	92 (82 to 100)	91 (80 to 100)

One study (N=108) reported on the diagnostic value of liver biopsy in alcoholic liver disease. A pre-biopsy clinical diagnosis of alcoholic liver disease (n=35) was confirmed by biopsy in all but one case. The specificity and sensitivity of a pre-biopsy diagnosis of alcoholic liver disease was 98% and 79% [77].

Level 1b

►***Alcohol-related hepatitis and cirrhosis***

One study asked four clinicians differing with respect to professional experience to make a diagnosis based on case history and blind of the biopsy results. They were also asked to rate the certainty of their diagnosis. The results for the diagnostic accuracy (number of patients, total N=200) of clinical compared with histological diagnosis for alcoholic cirrhosis versus no alcoholic cirrhosis are given in Table 3-3 below [76].

Level 1b

Table 3-3. Summary of results.

	Biopsy diagnosis	
Clinical diagnosis	Positive	Negative
Positive	65	13
Negative	15	107

The sensitivity of the clinical diagnosis was 81% (95%CI 73 to 99%)
The specificity of the clinical diagnosis was 89% (95%CI 84 to 95%)
The positive predictive value was 83% (95%CI 75 to 92%)
The negative predictive value was 88% (95%CI 82 to 94%).[76]

Level 1b

15 patients had a histological diagnosis of alcoholic cirrhosis but were given a negative clinical diagnosis (false-negative):

- 14/15 had steatosis
- 1/15 had acute viral hepatitis
- There was no incorrect clinical diagnosis (0/15) in those patients whom the clinicians were certain of their diagnosis.

Level 1b

13 patients were given a clinical diagnosis of alcoholic cirrhosis but the histology was negative (false positive):

- 4/13 showed steatosis with alcoholic hepatitis
- 5/13 showed steatosis
- 1/13 showed stasis hepatitis
- 2/13 had large-duct obstruction
- 1/13 had normal liver disease.

Level 1b

There was no statistical difference for the number of correct or incorrect clinical diagnosis according to professional experience:

- Chief physician N=3
- Senior resident N=5
- Resident N=4
- Junior resident N=7.[76]

Level 1b

The diagnostic accuracy of C-reactive protein (CRP) was reported for alcoholic hepatitis in heavy drinkers (N=101). 29/101 (30%) patients were diagnosed with alcoholic hepatitis on biopsy. Using optimized cut-off values (CRP > 19 mg/L) to discriminate between patients with alcoholic hepatitis and those without these histological lesions, the sensitivity, specificity, positive, negative predictive value and diagnostic accuracy were 41%, 99%, 92%, 81% and 82%, respectively [75].

Level 1b

One study (N=117) reported on whether raised gamma glutamyltranspeptidase (GGT) alone was a sufficient indication for performing liver biopsy. Patients with suspected alcoholic liver disease who had a liver biopsy were categorised in to three groups, namely raised GGT only (17/117, 15%), increased aspartate aminotransferase (AST) with or without raised GGT (34/117, 29%) or widespread abnormal liver function test (66/117, 56%). The following results were reported:

- 0/17 raised GGT has biopsy diagnosis of hepatitis or cirrhosis
- 5/34 (15%) with raised GGT and AST had hepatitis
- 3/34 (9%) had cirrhosis
- 13/66 (20%) with widespread abnormalities had hepatitis
- 14/66 (21%) had cirrhosis.[80]

Level 2+

One study (N=89) reported on patients with clinically mild biopsy-proven alcoholic hepatitis for a follow-up period of at least 30 months. Although clinical and laboratory abnormalities were minimal, cirrhosis was present in 38%. A decision rule based on the best predictors of cirrhosis (immunoglobulin A (IgA), prothrombin time and serum glutamic-oxaloacetic transaminase (SGOT)/serum glutamic pyruvic transaminase (SGPT)) was derived to predict the probability of being cirrhotic. The sensitivity was 72% and specificity 88%. [79]

Level 1b

One study (N=225) aimed to identify a panel of biomarkers (AshTest) for the diagnosis of alcoholic steato-hepatitis (ASH), in patients with chronic alcoholic liver disease. At a 0.50 cut-off, the sensitivity of AshTest was 0.80 and the specificity was 0.84%. [74]

Level 1b

One study selected patients with histologically classified alcoholic liver cirrhosis or alcoholic hepatitis and reclassified them using a likelihood method using 15 or 5

parameters (best combination based on stepwise regression) (see clinical methodology above). The diagnostic accuracy of using the first or second likelihood diagnosis is presented in Table 3-4 below[81].

Level 1b

Table 3-4. Diagnostic accuracy.

Group	Correct diagnosis rate of 1st likelihood diagnosis		Correct diagnosis rate of 1st or 2nd likelihood diagnosis	
	15 variables	**5 variables**	**15 variables**	**5 variables**
Alcoholic liver cirrhosis N=37	27.5 cases (74%)	30.5 (82)	34 (92%)	34 (92)
Alcoholic hepatitis N=14	10.5 (75%)	7 (50)	13 (93)	11 (79)

Safety of liver biopsy

►***Mortality***

Percutaneous:

In the largest study (N=68,276) the mortality rate was 0.009%.[83]

Level 3

Overall, the mortality rate ranged from 0 to 0.4% (N=10)

Transjugular/ transvenous:

Overall, the mortality rate ranged from 0.4 to 0.96% (N=2)

►***Bleeding***

Percutaneous:

In the largest study (N=68,276) (total, in patients with cirrhosis) [83]**:**

- Haemoperitoneum occurred in 0.032% and 0.031% of cases
- Intrahepatic haematoma occurred in 0.0059% and 0.004% of case
- Haemobilia occurred in 0.0059% and 0.004% of cases
- Haemothorax occurred in 0.018% to 0.022% of cases.

Level 3

The overall bleeding rate ranged from 0.06 to 1.7% (N=10).

Bleeding was reported to be higher in patients with increased INR (>1.5), raised bilirubin and lower platelet counts (150 x 10^{9}/l).[2] [87]

Level 3

[2] patients with an INR of 1.5 would not normally be considered for a straight percutaneous biopsy (occasionally ultrasound guided plugged biopsy).

Haemoperitoneum resulting in death was also higher in cirrhotic patients.[83]
Level 3

Transjugular/ transvenous:
The overall bleeding rate ranged from 0.96 to 3.3% (N=2).

One study reported that the majority of patients undergoing transjugular biopsy have contraindications for percutaneous liver biopsy such as coagulation abnormalities and ascites, therefore making them higher risk for bleeding and explaining the variation in bleeding rates between the two different biopsy techniques.[94]
Level 3

►**Perforation**
Percutaneous:
In the largest study (N=68,276) (total, in patients with cirrhosis)[83]:

- Pneumothorax occurred in 0.035% and 0.035% of cases
- Lung puncture occurred on 0.0015% and 0.004% of cases
- Colon puncture occurred in 0.004% and 0.004% of cases
- Kidney puncture occurred in 0.003% and 0% of cases
- Gallbladder puncture 0.012% and 0.013% of cases

Level 3

The overall rate of perforation ranged from 0.06 to 0.5% (N=2).

Transjugular/ transvenous:
The overall rate of perforation ranged from 0.6 to 5.8% (N=3)

The study reporting perforation in 5.8% of case consisted of the highest number of patients with cirrhosis (80.8%)[96].
Level 3

►***Infection***
Percutaneous:
In the largest study (N=68,276) (total, in patients with cirrhosis)[83]:

- sepsis occurred in a total of 0.0088% of cases and in 0.018% with cirrhosis.

Level 3

The overall infection rate ranged from < 0.0001% to 0.018% (N=2).

Transjugular/ transvenous:
Infection rate was not reported in two of the studies [95,96], and one study reported negative blood cultures in patients with pyrexia or rigors.[94]

Percutaneous biopsy:
Table 3-5shows the results according to date of the study:

Table 3-5. Summary of results.

	Date	Number of biopsies	Bleeding	Mortality	Perforation	Infection
PERRAULT [93]	1978	1000	0%	NR	NR	NR
PICCININO [83]	1986	68,276	Total 0.06% (of patients with cirrhosis: 0.3%)	Total 0.009%	Total 0.04% (of patients with cirrhosis: 0.06%)	Total 0.0088% (of patients with cirrhosis: 0.018%)
COLOMBO[86]	1988	1,192	0.25%	NR	NR	NR
MCGILL [84]	1990	9,212	0.38%	0.11%	NR	NR
MAHARAJ[85]	1992	2,646	0.3%	0.3%	NR	0.04%
DOUDS [92]	1995	546	1.5%	0.4%	NR	NR
GILMORE [87]	1995	1,500	1.7 %	0.13-0.33%	NR	NR
WAWRZYNOWICZ [91]	2002	861	0.6%	0%	0.5%	0.11%
FIRPI [89]	2005	3,214	0%	0.06%	NR	NR
VAN DER POORTEN [88]	2006	1,398	0.5%	0.13%	NR	NR
MANOLAKOPOULOS [90]	2007	631	0.3%	0%	NR	NR
MYERS [82]	2008	4,275	0.35%	0.14%	NR	< 0.0001%

NR = not reported

Transjugular biopsy:

Table 3-6shows the results according to the date of the study.

Table 3-6. Summary of results.

	Date	Number of biopsies	Bleeding	Mortality	Perforation	Infection
VELT [95]	1984	160	NR	NR	0.6%	NR
GAMBLE [95]	1985	436	3.3%	0.4%	3.9%	0%
VLAVIANOS [96]	1991	104	0.96%	0.96%	5.8%	NR

NR = not reported

3.1.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic evidence was identified assessing the cost-effectiveness of liver biopsy, and laboratory and clinical markers for the diagnosis of alcoholic liver disease. Costs associated with liver biopsy were presented to the GDG.

3.1.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

The two most commonly performed approaches for liver biopsy used in alcohol-related liver diseases are the percutaneous and the transjugular approaches. In England and Wales, a liver biopsy procedure can be performed as a day-case intervention or the patient being hospitalized. The cost for liver biopsy procedure is high (for the percutaneous approach, from £1,253 to £4,638 when the patient is hospitalised, considering possible complications and the inpatient stay; and from £437 to £490 when performed as a day-case intervention[97]. The transjugular approach is not available in all hospital in England and Wales, and patients need to be transferred to another hospital for the procedure. This involves additional costs.

3.1.6 FROM EVIDENCE TO RECOMMENDATIONS

The GDG recognised that the role of liver biopsy in ALD is not clear and that this is a complicated area. Practice differs throughout the country and the indications, modality and access are not uniform. We have attempted to give guidance in some areas that may affect practice.

First we discussed the safety of liver biopsy. There was a broad range of death and complication rates recorded for liver biopsy. Mortality ranged from 0 – 0.4% for percutaneous and 0.4 – 0.96% for transjugular/transvenous methods. The possible reasons for this broad range of results include the sample size, the period in which the data were collected, the patient populations and the type and the method (needle type, ultrasound guided versus non-ultrasound guided) used. For the outcomes of bleeding, infection and perforation the studies varied considerably with respect to how outcomes were defined. In spite of these differences, there were some large studies, and, on the whole, the GDG accepted the figures for mortality and major morbidity. The GDG felt that the true current figures are likely to be at the lower end of the reported risks for both transcutaneous and transvenous biopsy. Nevertheless, it is important to recognise that there are still mortalities from what is a diagnostic procedure.

The GDG then discussed the issue of sampling error. This is more important with regard to staging than diagnosis but it should be noted that data from twin biopsy studies in non-alcohol-related steatohepatitis (NASH) have shown variability throughout one liver[98] calling into question the role of liver biopsy as the 'gold standard' diagnostic and staging tool.

The GDG then spent some time discussing the context of the questions. It had been decided that they would not ask a question about the role of liver biopsy in the staging of ALD. This decision had been made for several reasons. First, the question does not

map directly to the scope of the guidance. Second, the question is not an alcohol-related liver disease question but more a general hepatology question. Third, studies have not yet been reported determining the role of non-invasive markers of fibrosis (such as fibroscan and serum markers) in ALD. As such the debate would not be informed and it would be difficult to make clear recommendations.

Some members of the GDG felt that it was very difficult to separate diagnosis from staging. They discussed the fact that in the real life clinical scenario, a patient with suspected ALD may have a biopsy for several reasons. This may be partly to exclude other conditions and confirm the diagnosis, partly to stage the disease and partly to demonstrate to the patient the severity of their condition in an effort to persuade them to remain or become abstinent. As such, the questions that have been posed do not answer the question of whether a patient with suspected ALD should have a liver biopsy or not. In order to do this we would need to have explored each of the proposed indications above. Rather, the recommendations will offer guidance as to whether the biopsy should be done for specific indications; to exclude other liver diseases and to confirm alcohol-related hepatitis before treatment.

In this complex area, a further issue was discussed outside of the questions and recommendations. This referred to the investigation of abnormal liver function in patients with a negative liver screen. The paper by Skelly et al[99] confirms that a significant proportion of these patients are found to have ALD and admit to drinking when further questioned. These data refer to the question of abnormal liver function with no obvious explanation. An inclusion criterion into this study was the denial of a strong alcohol history. Again, this issue has not been covered by our clinical questions. We recognise that liver biopsy has a role in the investigation of unexplained liver blood test abnormalities, but our question refers to the utility of liver biopsy in patients in whom there is a strong pre-clinical suspicion of ALD (through a typical history, appropriate laboratory tests and compatible imaging).

Studies looking at the accuracy of liver biopsy in the diagnosis of alcohol-related liver disease and non-alcohol-related liver diseases were of low to moderate quality. Patient populations varied considerably, particularly with respect to the non-alcohol liver disease populations (different aetiologies of liver disease).

Overall, if there was a high clinical suspicion of ALD and the liver screen (blood tests done to exclude other causes of liver disease) was negative the biopsy usually revealed ALD and rarely revealed other liver diseases. It must be highlighted again that this did not include patients in whom there was significant 'pre-biopsy' clinical doubt about the condition. When discussing these data, the GDG agreed that the issues surrounding biopsy can be complex and should be made by an experienced clinician. In addition, a full pre-biopsy work-up should be done to enable the most accurate clinical diagnosis to be made. These sentiments are reflected in the guidance. On balance, the GDG felt that if these conditions were adhered to, a biopsy was not required to confirm that alcohol was the cause of the liver disease and that there was no indication to do a liver biopsy solely to exclude other causes.

The GDG recognises that some clinicians will still undertake a biopsy for staging purposes as this can not be assured with certainty from indirect markers. It is particularly important to differentiate those patients with well compensated cirrhosis as they will require long-term surveillance for hepatocellular carcinoma.

When the GDG discussed the evidence for the role of liver biopsy in the differentiation of alcohol-related hepatitis from decompensated cirrhosis there were several important themes. The first was that the clinical (pre-biopsy) differentiation of alcohol-related hepatitis from decompensated cirrhosis is inaccurate. While there is a paucity of good studies, a combination of clinical data and GDG experience suggests that the sensitivity and specificity of a pre-biopsy suspicion of alcohol-related hepatitis is between 80 and 90% in those patients that have severe disease. These figures reflect the fact that, without a biopsy, it is difficult to determine which patients should have specific therapy. There are concerns, particularly with corticosteroids, that treatment of a suspected case of alcohol-related hepatitis may be detrimental to the patient if, in fact, they have decompensated cirrhosis. The second major theme of the discussion was that patients in this population often have contra-indications to percutaneous liver biopsy mandating the transjugular approach if biopsy is required. This has increased risks and current access to this procedure is limited to specialist centres. In spite of these concerns, it was felt that it was important to confirm by biopsy the clinical suspicion of alcohol related hepatitis in those patients that would require specific therapy. It was not felt to be imperative to delay treatment until the biopsy was done, but it was felt important to obtain a biopsy soon after presentation with the illness.

3.1.7 Recommendations

R18 For people with a history of harmful or hazardous drinking, who have abnormal liver function tests, exclude alternative causes of liver disease.

R19 A clinical diagnosis of alcohol-related liver disease or alcohol-related hepatitis should be confirmed by a specialist experienced in the management of alcohol-related liver disease.

R20 Take into account the small but definite risks of morbidity and mortality when deciding on the utility of liver biopsy in the investigation of alcohol-related liver disease or alcohol-related hepatitis. Discuss the benefits and harms of liver biopsy with the patient and ensure informed consent.

R21 In people with suspected acute alcohol-related hepatitis offer a liver biopsy to confirm the diagnosis if the hepatitis is severe enough to require specific therapy such as corticosteroids. Take into account factors such as access and safety.

3.2 REFERRAL FOR CONSIDERATION OF LIVER TRANSPLANTATION

3.2.1 CLINICAL INTRODUCTION

Since initial reports of success in the 1980s, alcohol-related cirrhosis has become an increasingly common indication for orthotropic liver transplantation. Several studies have convincingly demonstrated that the survival of patients transplanted for alcohol-related cirrhosis is comparable to patients with cirrhosis of alternative aetiologies [100]. Furthermore, there is no evidence that patients with alcohol-related liver disease have a higher frequency of post-operative complications.

However, transplantation for this condition still remains controversial, principally due to concerns over the risk of post-transplant recidivism and its effect on outcome and public opinion at a time of increasing donor shortage.

It is beyond the scope of these guidelines to determine the safety, efficacy or cost-effectiveness of liver transplantation for alcohol-related cirrhosis. In addition, it is not within the scope to write guidelines around which patients should be given access to this procedure. The principles of selection to a liver transplant list in the UK have recently been revised [101] and the assessment of co-morbidities and risk of recidivism are the role of the liver transplant units.

Table 3-7. Variant syndromes and definitions for selection to the adult elective liver transplant waiting list[101]

i. Diuretic resistant ascites	Ascites unresponsive to or intolerant of maximum diuretic dosage and non responsive to TIPS or where TIPS deemed impossible or contraindicated and in whom the UKELD score at registration is less than or equal to 49
ii. Hepatopulmonary syndrome	Aerial Po2 less than 7.8 kPa. Alveolar-arterial oxygen gradient less than 20 mm Hg. Calculated shunt fraction greater than 8% (brain uptake following technetium macro-aggregate almumin), pulmonary vascular dilation documented by positive contrast enhanced trans-thoracic echo in the absence of overt chronic lung disease.
iii. Chronic hepatic encephalopathy	Confirmed by EEG or trail making tests with at least two admissions in 1 year due to exacerbations of encephalopathy that has not been manageable by standard therapy. Structural or neurological disease must be excluded by appropriate imaging and if necessary paychometric testing.
iv. Persistent and intractable pruritus	Pruritus consequent on cholestatic liver disease which is intractable after therapeutic trials which might include cholestyramine, ursodeoycholic acid, rifampicin, ondansetron, naltrexone and after

	exclusion of psychiatric co-morbidity that might contribute to the itch.
v. Familial amyloidosis	Confirmed transthyretin mutation in the absence of significant debilitating cardiac involvement or autonomic neuropathy.
vi. Primary hyperlipidaemias	Homozygous familial hypercholesterolaemia with absent LDL receptor expression and LDL receptor gene mutation.
vii.Polycystic liver disease	Intractable symptoms due to the mass of liver or pain unresponsive to cystectomy or severe complications secondary to portal hypertension.

It is, however, within our scope to address the timing of referral for transplantation. It is likely that patients with alcohol-related cirrhosis are under-represented on transplant waiting lists given the prevalence of the condition compared to other aetiologies of cirrhosis. There are likely to be many reasons for this but awareness of both which patients to refer and when to refer them probably plays a significant role. Whom to refer is determined by the criteria for selection on to a transplant list (refer to Table 3-3), but the GDG believe the timing of referral with regard to the drinking history is critical. Further evidence of the need for recommendations comes from the geographical variability of referral of patients with ALD cirrhosis to liver units across the UK.

People who are still actively drinking alcohol are not candidates for referral. A period of abstinence is required for a variety of reasons. It is very important to satisfy public opinion (donated organs are a public resource) that the patient is trying to help themselves and there are some data that it associates with post-transplant abstinence but this is controversial. Most importantly, a period of abstinence may allow the liver to recover to a such a degree that transplantation is no longer necessary. Unfortunately, there is still controversy over what period of abstinence is necessary to achieve maximal improvement.

As such, the clinical question upon which the evidence was searched was:

> *What length of abstinence is needed to establish non-recovery of liver damage, which thereby necessitates referral for consideration for assessment for liver transplant?*

3.2.2 Clinical Methodological Introduction

One case series [102] was identified addressing the length of abstinence required to allow improvement in liver function. The study looked at the proportion of patients with severe alcoholic cirrhosis who would need a liver transplant and tried to determine the optimal time needed to evaluate an abstinent patient prior to referral for liver transplantation. All patients recruited for this study were presenting for the first time

with severely decompensated alcohol-related cirrhosis, classified as a Child-Pugh class C.

Level 3

Studies were excluded if they looked at the impact of abstinence or continued alcohol consumption on liver disease progression and reported survival as the only outcome.

The reliability of this evidence is poor as it is based on a single case series with a small sample size.

Level 3

3.2.3 Clinical Evidence Statements

►*Improvement of Liver Function*

One study [102] reported on a change in Child-Pugh score from C to B or A as a measure of improved liver function in abstinent patients. Improvement always began within three months if it occurred at all. See Table 3-8 below for a summary of results.

Table 3-9. Summary of results.

Study	Patient population	Intervention	Outcome measures	Improvement of liver function
Veldt et al. 2002[102] Retrospective/ prospective case series 3	N= 74 N=19 at follow up Patients that required admission to hospital for complications of a first episode of Child C cirrhosis of alcoholic origin	Abstinence Patients were considered as abstinent when they declared to be so and evolution of biological markers was in accordance.	Survival and transplantation Prognostic factors Improvement of liver function (Child-Pugh score improvement from C to B or A)	The rate of liver improvement in abstinent patients: - 1 month: 23% - 2 months: 40% - 3 months: 66% - 6 months: 66% Improvement in Child-Pugh score always began within 3 months if it occurred.

3.2.4 Health economic methodological introduction

There were no health economic studies found that pertained to the duration of abstinence. However we found one UK health technology assessment evaluating the cost-effectiveness of liver transplant for different patient groups. This study suggested that transplantation was not cost-effective for patients with alcoholic liver disease; if

this is true then it would preclude the need for the clinical question. Therefore we reviewed the study to establish the validity of this conclusion.

Longworth 2003[103] presented a cost-utility analysis (reporting cost per QALY gained) based on 1995-1996 prospective cohorts of transplanted patients treated for alcoholic liver disease (ALD, n=155), primary biliary cirrhosis (PBC, n=122), and primary sclerosing cholangitis (PSC, n=70). Comparative outcomes for patients not receiving the intervention (liver transplant) were obtained from patient-level pre-transplantation data and from prognostic models, which are based on historical cohorts of patients treated for PBC, ALD, or PSC. A UK NHS perspective was taken for this analysis. Cost and QALYs outcomes were estimated 27 months after a patient was placed on the liver transplant waiting list (approximately 24 months after the transplant procedure). Health outcomes considered for this analysis were survival and health-related quality-of-life (HRQL). HRQL was assessed using the EuroQol EQ-5D classification system, administered to patients at time of listing, at 3-month intervals until transplantation, and then at 3, 6, 12, and 24 months post-transplantation. Costs included were initial assessment for transplantation, hospitalisation, outpatient visits, drugs, blood products, nutrition, physiotherapy sessions, dietician sessions, tests, treatments, and the transplant operation (1999 GBP). Costs were discounted at 6% and QALYs at 1.5%. Extensive sensitivity analyses were undertaken.

3.2.5 HEALTH ECONOMIC EVIDENCE STATEMENT

As noted in 3.2.4 above there were no health economic studies found that pertained to the duration of abstinence.

Longworth 2003[103] reported incremental cost-effectiveness ratios for liver transplant of £48,000 per QALY gained for ALD patients, £29,000 per QALY gained for PBC patients, and £21,000 per QALY gained for PSC patients. The study considered the initial assessment cost and the time on the waiting list, this being integral components of the UK liver transplantation program. The cost for pre-transplant assessment influenced largely the result for ALD patients: "The larger incremental cost-per-QALY ratio for ALD patients is in part the influence of a larger proportion of ALD patients being considered unsuitable for transplantation after undergoing the assessment process. A reduction in the size of this group of patients, possibly through better evaluation of patients before assessment at transplant centres, would reduce the mean incremental cost-per-QALY ratio for the ALD group"[103]. In addition, the author mention that if calculated from the time of transplantation (i.e. excluding assessment costs), the incremental cost-effectiveness ratio would be over 50% lower.

This study showed that referring ALD patients for liver transplantation under the 1995-1996 system was not cost-effective and that better referral criteria in primary and secondary care would improve the cost-effectiveness ratio. Hence, the specifics of the referral process for liver transplant for ALD patients might have significant impact on service costs.

An important limitation of the study is that it measured cost-effectiveness of liver transplantation only up to 27 months from time of listing. A lifetime analysis is more

appropriate as mortality is impacted by the intervention. In addition, a longer time frame may better cover all costs and benefits related to the intervention, and is likely to increase the QALY gain and improve the cost-effectiveness ratio in favour of transplantation. Furthermore, clinical and resource use data were collected from a 1995-1996 prospective cohort. Discussions with clinical experts suggest that the current UK referral pathway is now much more selective and presumably more cost-effective than it was at the time of the study.

This study has significant limitations. The GDG felt that liver transplantation in its current form is likely to be cost-effective for ALD patients, when long-term benefits and modern selection practices are taken into account.

3.2.6 From evidence to recommendation

Only one small case series was reviewed[102] and limited results of interest were reported.

It was found that improvement in liver function, if it occurred at all following abstinence from alcohol, was always evident within three months. This is in agreement with the clinical experience of GDG members.

The paper reported on abstinent (those who declared they were abstinent and confirmed by biological markers), sober (those who decreased their consumption to a non-excessive level: less than 3 units per day for a man, 2 units for a woman; with normalisation of GGT and MCV) and relapsing (one or more periods of abstinence alternating with periods of excessive consumption) people. The GDG agreed that while the study findings were not in completely abstinent people, it was important to include the term 'abstinent' be included in the recommendation, particularly as it concerns the allocation of a public resource.

The health economic analysis by Longworth et al. conducted from a UK perspective concluded that liver transplantation was not cost-effective for alcohol liver disease patients, mainly because of the lack of selectivity of the 1995-1996 referral scheme, leading to important additional cost in assessing unsuitable patients for transplantation. The GDG agreed that optimising the selection of patients before assessment at transplant centres is essential, and noted that while the referral process may have led to a reduction in the number of people being inappropriately referred since 1995, there is still room for improvement. In addition, when a referred patient is seen at a transplant centre, there is a tendency to repeat many of the costly tests that have already been carried out, and an improvement in communication between the transplant centres and the referring hospitals may effect substantial cost savings.

3.2.7 Recommendations

R22 Refer for consideration for assessment for liver transplant a person who still has decompensated liver disease after best management and 3 months' abstinence, if they are otherwise suitable for liver transplantation.

3.3 CORTICOSTEROID TREATMENT FOR ALCOHOL-RELATED HEPATITIS

3.3.1 CLINICAL INTRODUCTION

Corticosteroids have been the most intensively studied of all treatments for acute alcohol-related hepatitis. They are used as anti-inflammatory agents in this acute inflammatory condition, but it is the potential side-effects, including poor wound healing and susceptibility to infection, that have made these drugs unpopular with some clinicians. These side effects are of particular concern as patients with severe alcohol-related hepatitis often die of sepsis or bleeding.

In order to determine their efficacy, corticosteroids have been delivered intravenously and orally for varying durations at varying doses in RCTs over the last 40 years. Results of these trials have, however, been conflicting and corticosteroids are used with varying frequency for this condition throughout the UK.

Before searching for and discussing trials assessing the efficacy of corticosteroids the GDG agreed that it was important to highlight the population of patients that would be considered for treatment. This is critical to the understanding of the history of corticosteroid use for this condition.

►Diagnosis

In many trials the diagnosis of alcohol-related hepatitis was not biopsy-proven. Many hepatologists believe this is a major omission particularly as evidence detailed earlier in this guideline has shown that this diagnosis can not always be made with certainty on clinical and laboratory evidence alone. Furthermore, it is easy to confuse the clinical picture of alcohol-related hepatitis with that of decompensated cirrhosis and these patients may do badly if inadvertently given corticosteroids. Only one corticosteroid treatment trial mandated biopsy but for purposes of this review it was decided not to exclude trials where biopsy was not undertaken in all patients. This was, however, borne in mind during the review of available evidence.

►Disease severity

The definition of severity has changed through the years. The presence of hepatic encephalopathy, severe coagulopathy and a high bilirubin were used in early studies. A major advance in the management of alcoholic related hepatitis came when Maddrey described the discriminant function (DF) (calculated from the prothrombin time and bilirubin) which correlates well with mortality[104]. Since this study, other scoring systems have been used, such as the Glasgow Alcoholic Hepatitis Score (GAHS) and the Model of End stage Liver Disease (MELD) score, but the discriminant function remains the one most widely used in the UK.

It was clear before we asked the clinical question that we would primarily be concentrating on patients with severe disease and we decided to use the Maddrey score of ≥32 to define this.

The GDG therefore asked the clinical question:

'In patients with acute alcohol-related hepatitis, what is the safety and efficacy of corticosteroids versus placebo?'

'What is the safety and efficacy of corticosteroids for acute alcohol-related hepatitis?'

3.3.2 CLINICAL METHODOLOGICAL INTRODUCTION

Eleven RCT's were identified that compared steroids with placebo or control treatment in patients with alcohol-related severe acute hepatitis [105; 106; 107; 108; 109; 110; 104; 111; 112; 113; 114]. One RCT was excluded for using a treatment regimen not currently used in clinical practice (methylprednisolone for 3 days [115]. For the sub-group analysis of patients with discriminate function (DF) greater than or equal to 32, data for one study [112] was taken from a paper reporting the results of an individual patients data analysis [116]. The studies published before Maddrey introduced the discriminant function criteria were included if the patients could be classified as severe alcohol-related hepatitis e.g., presence of spontaneous encephalopathy.

Level 1+

Table 3-10below summarises the inclusion criteria and treatment intervention for the included studies. Follow-up ranged from one and a half weeks to one year.

Table 3-10. Summary of inclusion criteria and treatment intervention for included studies.

Study	Inclusion criteria	Intervention (initial dose)	Duration of treatment
HELMAN 1971[105]	Subset with severe hepatitis	Prednisolone 40mg	4 weeks
PORTER 1971[106]	Severe	Methyl-prednisolone 40mg	10 days continued until improvement or tapered
CAMPRA 1973[107]	Severe	Prednisolone 0.5 mg/kg	6 weeks
BLITZER 1977[108]	Severe	Prednisolone 40mg	26 days
SHUMAKER 1978[109]	Subset with hepatic encephalopathy	Methyl-prednisolone	4 weeks

Study	Inclusion criteria	Intervention (initial dose)	Duration of treatment
		80mg	
LESESNE 1978[110]	Severe	Prednisolone 40mg	6 weeks
MADDREY 1978[104]	DF ≥ 32 or hepatic encephalopathy	Prednisolone 40mg	32 days
DEPEW 1980[111]	DF ≥ 32 or hepatic encephalopathy	Prednisolone 40mg	42 days
MENDENHALL 1984[112]	Subset with severe hepatitis	Prednisolone 60mg	30 days
CARITHERS 1989[113]	DF ≥ 32 or hepatic encephalopathy	Methyl-prednisolone 32mg	42 days
RAMOND 1992[114]	DF ≥ 32 or hepatic encephalopathy	Methyl-prednisolone 40 mg	28 days

The following outcomes were reported:

- All cause mortality follow-up one month
- All cause mortality follow-up six months
- Liver-related mortality follow-up one month
- Liver-related mortality follow-up six months
- Rate of Infection
- Rate of gastro-intestinal bleeding
- Length of stay

Where available, data is reported for all patients randomised. In some studies, data was available for all randomised patients for some outcomes only.

3.3.3 CLINICAL EVIDENCE STATEMENTS

Patients with DF ≥ 32, hepatic encephalopathy or severe hepatitis

For a summary of the results see Table 3-11below. See A.2for the forest plots.

Table 3-11. Summary of results.

	No. of studies	Risk Ratio (Mantel-Haenszel) M-H, Fixed, 95% CI)	Heterogeneity

Corticosteroids vs control			
All cause mortality – one month	7	0.45 (0.30 to 0.67); p<0.00001	4% p=0.40
All case mortality – six months –	11	0.54 (0.41 to 0.70); p<0.00001	53% p=0.02
Liver related mortality – one month	3	0.24 (0.09 to 0.62); P=0.003	0% p=0.61
Liver related mortality – six months	6	0.63 (0.41 to 0.97); p=0.04	36% p=0.04
GI bleeding	2	0.63 (0.21 to 1.96); p=0.43	69% p=0.07
Infection	4	1.14 (0.72 to 1.81) P=0.46	0% p=0.58

Level 1+

►Length of stay

Two studies reported on this outcome [111]; [107]. None of the studies provides confidence intervals and therefore the data could not be entered into a meta analysis. See Table 3-12 for a summary of results.

Level 1+

Table 3-12. Summary of results.

Study	Steroid	Control	P value
DEPEW[111]	65.6	56.2	NR
CAMPRA[107]	47	48	NR

Summary

For patients with severe hepatitis, DF ≥ 32 or hepatic encephalopathy, steroids were associated with a significant reduction in the following compared to control:

- All cause mortality follow-up one month
- All cause mortality follow-up six months (with significant heterogeneity)
- Liver-related mortality follow-up one month

- Liver-related mortality follow-up six months

There were no significant differences between steroids and control for:

- Infection rate
- Gastro-intestinal bleeding

Note, that the estimate of effect for liver-related mortality at one and six months and for the rates of infection and GI bleeding are 'imprecise' (wide confidence intervals).

Level 1+

Patients with DF ≥ 32

Table 3-13below summarises the results for patients with DF ≥ 32. See A.2for the forest plots.

Table 3-13. Summary of results.

	No. of studies	Risk Ratio (M-H, Fixed, 95% CI) corticosteroids versus control	Heterogeneity
All cause mortality – one month	4	0.42 (0.26, 0.69); p=0.0006	35% p=0.20
All case mortality – six months	4	0.38 (0.23, 0.61); p=<0.0001	52% p=0.10
Liver related mortality – one month	2	0.17 (0.03, 0.87); p=0.03	0% p=0.45
Liver related mortality – six months	2	0.52 (0.11, 1.02); p=0.05	45% p=0.18

►Length of stay

No studies reported on this outcome for this patient population.

►Gastrointestinal bleeding

No studies reported on this outcome for this patient population.

►Infection

One study reported no cases of infection associated with corticosteroids or placebo [104].

Summary

For patients with severed alcoholic hepatitis defined as DF ≥ 32, steroids were associated with a significant reduction in the following compared to control:

- All cause mortality follow-up one month
- All cause mortality follow-up six months
- Liver-related mortality follow-up one month

There were no significant differences between steroids and control for:

- Liver-related mortality follow-up six months

3.3.4 *HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION*

No relevant economic analysis was identified assessing the cost-effectiveness of corticosteroids in patients with acute alcohol-related hepatitis**.** The cost of oral corticosteroids was presented to the GDG.

3.3.5 *HEALTH ECONOMIC EVIDENCE STATEMENTS*

The cost of oral corticosteroids is low (few pence per dose [prednisolone][117]). The effect of this therapy on the hospital length of stay was not conclusive from the clinical review. With regard to the cost of the drug treatment, the cost-impact of treating patients with acute alcohol-related hepatitis with oral corticosteroids is likely to be marginal.

3.3.6 *EVIDENCE TO RECOMMENDATIONS*

The GDG discussed the variability in the trials. The early studies included many patients with mild disease and did not mandate liver biopsy. Some studies used the development of spontaneous hepatic encephalopathy as a marker of severity but this syndrome may develop in patients with decompensated cirrhosis per se. The analysis was restricted to those trials using oral corticosteroids but even within these the periods of treatment were not uniform.

To allow the use of data from before the Maddrey study in 1978 the definition of severity was a DF of≥32 **or** the development of spontaneous hepatic encephalopathy. In addition, the data were analysed using only DF≥32 as a marker of severity. This restricted the trials that could be included but the GDG felt it was a more accurate assessment of disease severity.

The GDG noted the efficacy of corticosteroids to reduce one and six month mortality using both definitions of severe disease. In addition there was no significant increase in bleeding or sepsis. The GDG felt that it was appropriate to recommend corticosteroids for patients with severe disease and that the Maddrey score of 32 should be the cut-off to define this. Encephalopathy was not included as a marker of severity in the recommendation as the GDG felt that they did not have robust evidence to recommend corticosteroids to a population with a DF <32 and encephalopathy.

The GDG did not include contraindications to corticosteroids in their recommendation. Gastrointestinal bleeding and active infection are generally considered to be contraindications and have been associated with a poorer outcome. It was agreed by the group that controlled bleeding should not be a contraindication. There is now

evidence that if confirmed infection is treated and corticosteroids are started, the outcome is unaffected. If bleeding or infection are present they should be treated appropriately and corticosteroids should still be used as the treatment for the liver condition.

Given the modest drug cost and the substantial reduction in mortality we expect corticosteroids to be highly cost-effective in appropriately selected patients.

3.3.7 RECOMMENDATIONS

R23 Treat with corticosteroids people with acute severe alcohol-related hepatitis and a discriminant function of 32 or more.

3.4 NUTRITIONAL SUPPORT

3.4.1 CLINICAL INTRODUCTION

Patients with acute alcohol-related liver disease are often malnourished and this has a detrimental effect on survival[112]. Initial trials with parenteral amino acid therapy yielded conflicting results in improving survival[118,119], but more recently the emphasis has switched to providing enteral nutrition. As well as providing calories and protein it is postulated that enteral feeding also provides specific therapy to the underlying inflammatory condition. Alcohol increases gut permeability and the subsequent portal endotoxinaemia can result in lipopolysaccharide-induced cytokine release from liver macrophages and hepatic inflammation. Enteral feeding can improve this gut permeability and this may be a mode through which the therapy can have an impact on liver inflammation and, ultimately, the outcome of an episode of acute alcohol-related hepatitis.

The exact role of enteral nutrition and whether it should be provided with another treatment or as monotherapy is not clear. Certainly, enteral nutrition is not used as standard therapy in all hospitals in the UK who manage this condition. For this reason, we asked the clinical question:

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

3.4.2 CLINICAL METHODOLOGICAL INTRODUCTION

Studies were included that reported on the safety and efficacy of enteral nutrition versus standard diet (hospital diet); enteral nutrition versus corticosteroids; enteral nutrition in combination with corticosteroids versus enteral diet in patients with acute alcohol-related hepatitis. Outcomes of interest were survival and adverse events from corticosteroids.

Three RCTs [120-122] and one non-randomised-control trial were included in the review [123].

Outcomes reported were mortality, length of stay, weight change and adverse events/side effects, including infections, hepatic encephalopathy, GI bleeding, diarrhoea and ascites.

The studies were reported under the following categories:

1. enteral nutrition versus standard diet (n=3)
2. enteral nutrition versus corticosteroids (n=1)

No studies were found that reported on the comparison enteral nutrition in combination with corticosteroids versus enteral diet.

In two studies [121,123] patients allocated to the standard diet group had significantly lower protein, nitrogen balance and calorie intake compared to patients in the enteral nutrition group[3,4]. Therefore, in effect the comparison could be seen to be adequate enteral nutrition versus inadequate oral nutrition.

Two of the studies [120,121] included patients with alcohol-related cirrhosis.

3.4.3 CLINICAL EVIDENCE STATEMENTS

Enteral nutrition versus standard diet (n=3)

►***Mortality***

All three studies reported on mortality in patients on enteral nutrition versus standard diet [121-123]. The Figure 3-1. shows the meta-analysed results, showing a non-significant (albeit borderline) reduction in mortality with enteral nutrition compared to standard diet.

Figure 3-1.

[3] Kearns 1992: Protein per day: enteral group: 103 ± 6g; standard diet group: 50 ± 4g , p<0.02; average nitrogen balance: enteral group: 480 mmol, standard diet group: 107 mmol; amount of resting energy expenditure (REE) consumed: enteral group: 1.7 ± 0.3 times their REE in first 2 weeks, standard diet group: 0.8 ± 0.1 of their REE in first 2 weeks.

[4] Mendenhall 1985: During 30 days hospitalization, calorie intake (kcal/day): standard diet: 2313 ± 121; enteral group: 3236 ± 102, p=0.0001; protein intake (g/day): standard diet: 81.3 ± 4.6; enteral group: 98.3 ± 3.5, p=0.05

Level 1+

►***Length of stay***

One study reported on the difference in length of hospital stay between the groups enteral nutrition versus standard diet[121].

- Enteral group: 11 days; standard diet group: 12 days

Level 1+

►***Weight change***

One study reported on weight change in both groups during the two week study period [121], with a significant decrease in weight reported in the standard diet group, and a non-significant decrease in the enteral nutrition group:

- Enteral nutrition group:74 ± 4 to 72 ± 5 kg, MD 2.00 [-0.57, 4.57], P=0.13
- Standard diet group:78 ± 3 to 72 ± 4 MD 6.00 [3.47, 8.53], P<0.001

Level 1+

►***Diarrhoea***

Two studies reported on the difference in the number of cases of diarrhoea between the groups enteral nutrition versus standard diet[121,122].

One study reported no cases in either group [122].

Level 1+

One study reported a non-significantly lower number of cases of diarrhoea in the enteral nutrition group compared to the standard diet group [121]:

- Enteral nutrition group 5/16 versus Standard diet group 6/15, RR 0.78 (0.30, 2.03), P=0.61

Level 1+

►***Hepatic encephalopathy***

Three studies reported on the difference in the number of cases of hepatic encephalopathy between the groups enteral nutrition versus standard diet [121-123].

One study reported no cases of hepatic encephalopathy associated with the enteral nutrition group [122].

Level 1+

One study [121] reported a significant improvement in the mean grade of encephalopathy over the nine week trial period in the enteral nutrition group:

- ± 0.3 to 0.4 ± 0.2, MD 0.70 (0.52, 0.88), p<0.001

With significant deterioration in the mean grade of encephalopathy over the 9 week trial period in the standard diet group:

- 0.7 ± 0.2 to 0.9 ± 0.3, MD -0.20 (-0.38, -0.02), p=0.03

  Level 1+

One study reported on the difference in portal systemic encephalopathy between the groups enteral nutrition versus standard diet [123].

There were a non-significantly higher number of post-therapy cases in the standard diet group compared to enteral nutrition group:

- Post therapy: Nutritional support group: 4/14 (29); standard diet group: 6/27 (59), RR 1.29 (0.43, 3.82)

There was a significant increase in the number of cases seen pre-therapy compared to post-therapy in the standard diet group:

- Standard diet group: pre versus post treatment: 21/34 (62) versus 6/27 (59), RR 2.78 (1.31, 5.91), P=0.008

There was a significant reduction in the number of cases seen pre-therapy compared to post-therapy in the enteral nutrition group:

- Nutritional support group: pre versus post treatment: 13/18 (72) versus 4/14 (29); RR 2.53 (1.05, 6.07), P=0.04

  Level 1+

►***Ascites***

One study reported on the difference in the number of cases of ascites between the groups enteral nutrition versus standard diet [123].

There were a non-significantly higher number of post-therapy cases in the standard diet group compared to enteral nutrition group:

- post therapy: nutritional support group: 7/14 (50); standard diet group: 16/27 (59), RR 0.84 (0.46, 1.55), p=0.59

There was a significant reduction in the number of cases seen pre-therapy compared to post-therapy in the standard diet group:

- standard diet group: pre versus post treatment: 29/34 (85) versus 16/27 (59), RR 1.44 (1.02, 2.03), P=0.04

There was a significant reduction in the number of cases seen pre-therapy compared to post-therapy in the enteral nutrition group:

- nutritional support group: pre versus post treatment: 16/18 (89) versus 7/14 (50); RR 1.78 (1.03, 3.08), P=0.04

Enteral nutrition versus corticosteroids

►***Mortality***

One study reported on mortality (as per protocol) in patients on enteral nutrition versus corticosteroids [120].

There was a non-significant increase in mortality in the enteral nutrition group compared to the corticosteroid group during the treatment period:

- Treatment period: enteral group: 10/27, corticosteroid group: 9/36; RR 1.48 (0.70, 3.14), P=0.30

There was a non-significant reduction in mortality in the enteral nutrition group compared to the corticosteroid group during the follow up period (1 year or until death):

- Follow up: enteral group: 1/17, corticosteroid group: 10/27; RR 0.16 (0.02, 1.13), p=0.07

  Level 1+

►***Length of stay (hospitalization)***

One study reported on the difference in the length of stay between patients on enteral nutrition versus corticosteroids [120]. There was a non-significant reduction in length of stay in the enteral nutrition group compared to the corticosteroid group:

- enteral group: 5.3 ± 12.3, corticosteroid group: 8.6 ± 13.6 Mean difference -3.30 (-9.33, 2.73), p=0.28

  Level 1+

►***Infections***

One study reported on infections in patients on enteral nutrition versus corticosteroids [120]. There was a non-significant increase in infections in the enteral nutrition group compared to the corticosteroid group:

- enteral group: 15/35; corticosteroid group: 14/36; RR 1.10 (0.63, 1.93), P=0.73
  Level 1+

►***Side effects***

One study reported on side effects in patients on enteral nutrition versus corticosteroids [120]. There was a non-significant increase in side effects in the enteral nutrition group compared to the corticosteroid group:

- enteral group: 10/35, corticosteroid group: 5/36; RR 2.06 (0.78, 5.41), P=0.14
  Level 1+

Summary

►***Enteral nutrition versus standard diet (n=3)***

Enteral nutrition resulted in a significant improvement in:

- Mean grade of encephalopathy [121]

Enteral nutrition resulted in a significant reduction in:

- Portal systemic encephalopathy [123]
- Ascites [123]

Enteral nutrition resulted in a non-significant reduction in:

- Mortality[121-123]
- Weight [121]
- Diarrhoea (compared to standard diet group) [121]

►***Enteral nutrition versus corticosteroids (n=1)***

Enteral nutrition resulted in a non-significant reduction in:

- Mortality at follow up [120]
- Length of stay [120]

Enteral nutrition resulted in a non-significant increase in:

- Mortality during treatment period [120]
- Infections [120]
- Side effects [120]

3.4.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis was identified assessing the cost-effectiveness of corticosteroids, standard diet, and enteral nutrition in patients with acute alcohol-related hepatitis**.** Costs of oral corticosteroids and of enteral nutrition were presented to the GDG.

3.4.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

The cost of oral corticosteroids is low (few pence per dose [prednisolone][117]). No direct cost evidence was found on the use of enteral nutrition in patients with acute alcohol-related hepatitis. The use of enteral nutrition was costed in one randomized controlled trial conducted in the United Kingdom assessing patients with severe acute pancreatitis[124]. The cost of enteral nutrition was reported to be £55 per patient when given for a median of 2 days (2-7). The study reported no complication associated with the use of enteral nutrition.

3.4.6 EVIDENCE TO RECOMMENDATIONS

The GDG accepted the limitations of the clinical evidence. Evidence that enteral nutrition consistently improved outcomes as monotherapy or in combination with other therapies in severe alcohol-related hepatitis was not available.

The studies comparing enteral nutrition to placebo showed reduction in mortality but this was not significant and the meta-analysis although showing a similar trend also failed to reach significance. The heterogeneity of the patient populations complicates the evidence, particularly since the studies concentrating on patients with alcohol-related hepatitis were less convincing than the study in patients with decompensated cirrhosis.

The study comparing enteral nutrition to corticosteroids is not adequate to determine whether there is a difference between the efficacy of corticosteroids and nutrition in the early phase or in follow up but the pattern of mortality during the trial fits conceptually with the action of each treatment and made us ask the question of what enteral nutrition may add to corticosteroid therapy in this population.

The GDG emphasised the importance of further trials in this area and this is reflected in the research recommendation. In addition, the evidence to date, though weak, is in support of the consensus that enteral tube feeding improved outcomes in patients with alcohol-related hepatitis.

3.4.7 RECOMMENDATIONS

R24 Provide enteral nutritional support to people with acute alcohol-related hepatitis.

3.4.8 RESEARCH RECOMMENDATIONS

RR5. 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?

3 ALCOHOL-RELATED PANCREATITIS

Prolonged hazardous drinking can result in progressive and irreversible damage to the pancreas gland. This occurs on the background of pancreatic inflammation, acinar atrophy and, ultimately, fibrosis and can result in significant exocrine and endocrine insufficiency. Some individuals may develop this condition with alcohol intakes as low as 20 g/day; others may need to drink in excess of 200 g/day before evidence of the disease develops; others may never develop this condition no matter how much they drink or for how long. In susceptible individuals the longer the duration of drinking the greater the risk of developing significant pathology.

Acute alcohol-related pancreatitis may present as an acute episode of abdominal pain, nausea and vomiting and in severe cases can be accompanied by profound metabolic abnormalities and circulatory collapse. These acute episodes may recur, often precipitated by an increase in alcohol intake. Complications such as narrowing of the common bile duct, localized leakage of pancreatic fluid and pancreatic exocrine and endocrine insufficiency may develop resulting in jaundice, pseudocyst formation, malabsorption and diabetes. In some individuals, however, the clinical course is insidious with progression to pancreatic insufficiency without acute inflammatory episodes.

The major clinical features of chronic pancreatitis are abdominal pain coupled with malabsorption/maldigestion and diabetes resulting from the exocrine and endocrine insufficiency. The stages and natural history of alcohol-related chronic pancreatitis have been difficult to characterize due to the fact that patients may present having suffered from symptoms for varying periods of time. In addition, the pancreas is rarely biopsied unless malignancy is suspected. Nevertheless, withdrawal of alcohol at an early stage may arrest the process and, even when the condition is established, may reduce the number of inflammatory episodes and allow for better control of both exocrine and endocrine insufficiencies.

3.1 DIAGNOSIS OF CHRONIC PANCREATITIS

3.1.1 CLINICAL INTRODUCTION

The diagnosis of chronic pancreatitis is based on relevant symptoms, imaging and the assessment of pancreatic function. Histological diagnosis requires a biopsy, which is rarely available. With specific treatments available for pancreatic pain and insufficiencies it is important to investigate appropriately and to confirm the diagnosis as early as possible in the pathogenic process.

The clinical question asked and upon which the literature was searched was:

"What is the diagnostic accuracy of abdominal ultrasound versus computed tomography (CT) for the diagnosis of alcohol-related chronic pancreatitis?"

3.1.2 CLINICAL METHODOLOGICAL INTRODUCTION

Three studies were identified that reported on the diagnostic accuracy of CT and abdominal ultrasound in patients with chronic pancreatitis [125]; [126]; [127]. Papers were excluded if they reported on either CT *or* ultrasound but not both. None of the papers reported the results of patients with alcohol-related chronic pancreatitis separate from other aetiologies of chronic pancreatitis. The three studies varied with respect to the patient population and the 'gold standard' used for diagnosis. See Table 3-1 for further details.

Level 1b

Table 3-1. Summary of included studies.

Bibliographic reference	No. of patients	Prevalence	Patient characteristics	Type of test	Reference standard
SWOBODNIK 1983[126] Prospective	N=75	27/75 (36%) chronic pancreatitis	Patients referred for endoscopic retrograde cholangiopancreatography (ERCP) with suspected pancreatitis Male:female 42:33, mean age 49 yrs	Ultrasound CT	73% laboratory data, functional tests and morphological imaging and 6 month to 1 year follow-up 27% final diagnosis confirmed by laparotomy or autopsy
ROSCH 2000[127] Retrospective	N=184	53/184 (29%) Chronic pancreatitis without focal inflammatory	Inpatients referred for suspected pancreatitis Male:female 111:73, mean age 56 yrs	Clinical assessment (laboratory findings plus ultrasound)	Surgery, histology and cytology plus information from one year follow-up

		mass; 18/184 (10%) Chronic pancreatitis with inflammatory mass 77/184 pancreatic malignancy (42%)		CT	
BUSCAIL 1995[125] Prospective	N=81	44/81 (54%) diagnosed with chronic pancreatitis	Patients referred for suspected pancreatitis Chronic pancreatitis With calcifications: male:female 22:2, mean age 48 years, clinical symptoms: abdominal pain and/or weight loss 22/24 Alcohol aetiology 24/24 Without calcifications: With calcifications: male:female 17:3, mean age 47 years, clinical symptoms: abdominal pain and/or weight loss 16/20, pain and jaundice 2/20, alcohol aetiology 20/20	Ultrasound CT	Diagnosis based on clinical, biochemical and CT, abdominal ultrasound, endoscopic ultrasonography and ERCP

1
2

3 *3.1.3 CLINICAL EVIDENCE STATEMENTS*

4 Table 3-2 below summarises the results for the three studies
5

6 **Table 3-2. Summary of results.**

Study	CT		Ultrasound	
	Specificity	Sensitivity	Specificity	Sensitivity
BUSCAIL 1995[125] Chronic pancreatitis (patients with and without calcifications)	75%	95%	58%	75%
ROSCH 2000 [127] Pancreatic disease versus normal pancreas	91%	78%	94%[1]	35%

SWOBODNIK 1983[126] Chronic pancreatitis	98%	74%	100%	52%

[1] Clinical assessment - laboratory values and ultrasound results

Level 1b

3.1.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis was identified that assessed the cost-effectiveness of abdominal ultrasound and computed tomography scan for the diagnosis of alcohol-related chronic pancreatitis. The cost of the procedures in England and Wales were presented to the GDG.

3.1.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

In England and Wales, computed tomography scans (two areas with contrast) are approximately twice as expensive as ultrasound scans: the national average unit cost varies from £96 to £125 per procedure for computed tomography scans and from £45 to £64 per procedure for ultrasound scans [97].

Even though CT scans are more expensive they may well be cost-effective or even cost saving compared with ultrasound in patients where there is a high clinical suspicion since they are far more sensitive at diagnosing chronic pancreatitis and have a high level of specificity (3.1.3).

We believe that in current practice, a patient would usually be offered a CT scan in specialist clinical practice (based on history and symptoms), but would more likely get an ultrasound in primary care due to easier access. However, the use of CT scans as the first-line imaging modality to diagnose chronic alcohol-related pancreatitis in patients with a suggestive history and symptoms might be more cost-effective. However, this might require direct access to CT scans for primary care practices.

3.1.6 EVIDENCE TO RECOMMENDATIONS

Before reviewing the evidence the GDG discussed the difficulty in writing guidance for the diagnosis of chronic alcohol-related pancreatitis. Chronic pancreatitis is characterised by progressive irreversible damage that ultimately results in both endocrine and exocrine insufficiency , and structural abnormality of the pancreas. The extent of each of these will vary between patients. The GDG concluded that no single test will give all of the information needed to make a diagnosis. Rather, an assessment of structure and function is required and this is reflected in the first recommendation.

When reviewing the evidence for ultrasound scan (USS) versus CT for the diagnosis of chronic pancreatitis, the GDG felt that there was an important differentiation to make:

abdominal USS is a good first line test in patients with abdominal pain of unknown aetiology, however, if the history and symptoms suggest chronic pancreatitis, (if the index of suspicion is high), USS does not have comparable sensitivity and a CT should be the first line investigation. This is reflected in the second recommendation.

3.1.7 RECOMMENDATIONS

R25 Use the combination of symptoms, an imaging modality to determine pancreatic structure and tests of pancreatic exocrine and endocrine function to inform a diagnosis of chronic alcohol-related pancreatitis.

R26 Use computed tomography as the first-line imaging modality for the diagnosis of chronic alcohol-related pancreatitis.

3.2 DIAGNOSIS OF ACUTE PANCREATITIS

The comparison of diagnostic tools used to obtain a acute pancreatitis was included the scope of this guideline, however, due to time constraints it was de-prioritised for literature review. The GDG refer you to the publication issued by the UK working party on acute pancreatitis publication titled 'UK guidelines for the management of pancreatitis'[128] for further information in this area.

3.3 PANCREATIC SURGERY VERSUS ENDOSCOPY

3.3.1 CLINICAL INTRODUCTION

The most troublesome symptom of chronic alcohol-related pancreatitis is pain. This pain is usually epigastric and may radiate to the back and flanks. It can be intermittent or continuous, and may alleviate late in the natural history; possibly associated with the loss in pancreatic exocrine function. Patients with chronic pancreatitis may, in addition to the pain they experience intrinsic to the disease itself, also develop pain in association with episodes of acute pancreatitis, formation of pseudocysts or associated conditions such as peptic ulceration. However, it is the pain of chronic pancreatitis to which we refer in this guideline. In spite of the varying aetiologies of chronic pancreatitis, the presenting symptoms are the same. As such the evidence was taken from studies of all types of chronic pancreatitis.

It is important to encourage abstinence from alcohol in this patient population. Abstinence probably reduces the severity of the pain and improves the response to treatment. Typically, pain is managed with simple analgesics but the dosage and strength of these may need to be increased over time. Many patients require high doses of opiates to control pain at its worst. However there are now a number of interventional procedures that can also be used to treat pain in this population. These range from nerve block/destruction (coeliac plexus block and thoracoscopic splanchnicectomy) to pancreatic endotherapy and surgery.

It was the aim of the GDG to determine which of these interventional therapies was most effective in the management of pain in this patient population. In addition, they aimed to determine the most appropriate timing for these procedures and whether they were best performed early in the natural history or later, after, for instance, analgesic failure. The following clinical questions were asked and upon which the literature was searched:

1) 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?
2) 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?
3) 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?
4) 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?

3.3.2 CLINICAL METHODOLOGICAL INTRODUCTION

The following studies were identified:

- One paper incorporating two case-control studies comparing coeliac plexus block with splanchnicectomy [129].
  Level 2+

- Two RCTs comparing surgery with endoscopic procedures [130,131]
  Level 1+

- Two prospective cohorts comparing surgery with conservative management (no surgery) [132,133]
  Level 2+

- One prospective case series comparing surgery with patients on opioids and one with those not on opioids (patients who are not on opioids are likely to be younger with a shorter duration of illness than those not on opioids and may therefore represent an early versus late surgery comparison) [134]
  Level 2+

Coeliac plexus block versus splanchnicectomy

One study, based on two non-randomised, prospective, case control studies compared patients with chronic pancreatitis treated with neurolytic coeliac plexus block (NCPB) or videothorascopic splanchnicectomy (VERSUSPL) in both of which the control patients were

managed conservatively [129]. In both studies, the patient 'chose the procedure according to their needs'. The two studies differed with respect to the quality of life measures used. A meta-analysis was performed on the data, but no details of heterogeneity were reported. Important methodological aspects of the study include:

- Non-randomised design
- the patients chose which intervention to undergo
- small sample size
- limited reporting of clinical and demographical variables at baseline
- analyses did not including confounding variables or adjust for baseline differences

Level 2+

Surgery versus conservative management

Two prospective cohort studies compared patients with chronic pancreatitis who underwent surgery with patients who did not undergo surgery [133]; [132]. The studies differed with respect to patient population, surgical intervention and length of follow-up. Importantly, patients who underwent surgery may represent a more severe end of the disease spectrum than those who did not undergo surgery. In one study, disabling pain was present in all patients who were operated on, but in only 28/44 (64%) of patients who were not operated on [133]. No details of any differences between patients who were operated on compared with those who were not were reported in the remaining study [132]. One additional prospective cohort study compared patients who were on opioids prior to surgery with those who were not on opioids [134].

Level 2+

Surgery versus endoscopy

Two RCTs were identified that compared surgery with endoscopic interventions [131],[130]. In the Dite study, 72 patients were randomised and an additional 68 patients chose whether to undergo surgery or endoscopic treatment. The two studies differed with respect to both interventions. In the Dite study, 80% of patients opting for surgery underwent resection. In the Cahen study, all patients underwent a drainage procedure. The Dite study tailored the surgery to the individual. In comparison to the Cahen study, the Dite study did not use shock-wave lithotripsy, cumulative stenting or repeated treatment after recurrence of symptoms

Level 1+

3.3.3 *CLINICAL EVIDENCE STATEMENTS*

Coeliac plexus block versus splanchnicectomy

►***Pain and quality of life***

Table 3-3below shows that at eight-week follow-up both treatments reduced pain, but VERSUSPL was more effective than NCPB. Physical well-being and fatigue also improved with treatment compared to conservative management but with little difference between the two treatments. Note, the follow-up period was relatively short [129].

Level 2+

Table 3-3. Summary of results.

Outcome	VERSUSPL (n=18) mean effect (compared with control) (95%CI)	NCPB (n=30) mean effect (compared with control) (95%CI)
Pain (VAS) 0 to 100% severe pain	15.82 (14.68 to 16.96)	8.89 (8.30 to 9.48)
Physical well-being	1.81 (1.57 to 2.06)	2.19 (2.96 to 2.42)
Emotional well-being	0.08 (-0.11 to 0.29)	3.55 (3.27 to 3.84)
Fatigue	2.52 (2.25 to 2.79)	6.87 (6.39 to 7.34)
Ailments typical for the illness	0.05 (-0.14 to 0.26)	0.64 (0.45 to 0.83)

►***Opioid use***

There was no statistical difference in the proportion of patients who underwent NCPB and VERSUSPL for:

- Opioid withdrawal (8/18 (47%) versus 11/30 (36%); RR1.21; 95%CI 0.60 to 2.44; p=0.59)
- Reduction in opioid dose (9/18 (53%) versus 14/30(45%); RR1.07; 95%CI 0.59 to 1.95; p=0.82)[129]

Level 2+

►***Adverse events/complications***

Orthostatic hypotension was observed for three days in 9/30 (30%) from the NCPB group and in 1/18 (5.5%) patients in the VERSUSPL group (RR5.40; 95%CI 0.74 to 39.17; p=0.10). Intermittent intercostal pain was treated with paracetamol for two weeks in 4/18 (22%) patients in the VERSUSPL group. In one of these, an intercostal nerve block was performed and in one patient a classic thoracotomy was performed due to massive adhesions (excluded from study) [129].

Level 2+

►***Mortality***

No cases reported [129].

Level 2+

Surgery versus conservative management

►***Pain***

One study reported a significant reduction in pain in patients who underwent surgery compared to those managed conservatively:

- Disabling abdominal pain (28/44 (64%) versus 41/41 (100%); RR0.64; 95%CI 0.51 to 0.90; p<0.00001) [133].

A second study reported no significant difference in pain in the surgery group compared with the conservative management group:

- pain disappeared or distinctly subsided immediately after operation in 62/70 (89%) patients with full documentation of the postoperative course: 40 had pain relief for a mean of 6.3 (± 4.5) years, but pain relapse occurred in 22 (36%) patients 1.6 ± 2 years after the operation. There was no significant difference in the pain course between operated and non-operated patients (p=0.61) [132]
  Level 2+

►***Weight gain***

One study reported on this outcome.

A significantly higher proportion of patients who underwent surgery compared with those who did not:

- gained weight (25/30 [87%] versus 5/38 [13%]; RR6.33; 95CI 2.76 to 14.56; p<0.00001) and the mean weight gained was significantly higher (4.2 kg [1.4 to 12.7] versus 0.50 kg [-3.6 to 2.7]; p<0.05)[133].
  Level 2+

►***Pancreatic function***

At follow-up there was a significant difference between the surgery and no surgery groups for the proportion of patients who remained at the same grade of mild to moderate (sustained pancreatic function) (16/19 [84%] versus 7/24 [29%]; RR2.89; 95%CI 1.50 to 5.55; p=0.001) or who progressed to 'severe' (3/19 [16%]versus 17/24 [71%]; RR0.22; 95%CI 0.08 to 0.65; p=0.006) [133].
Level 2+

►***Mortality***

- One operative death occurred [133].
  Level 2+

- Three patients died within eight weeks of surgery. Three further patients died of hypoglycaemia [132].
  Level 2+

►***Complications***

Three patient had wound infections [133].
Level 2+

Surgery plus previous opioid use versus surgery with no previous opioid use

One prospective cohort reported on the outcomes of patients following pancreatic resection in patients with prior opioid use [134].
Level 3

►***Group differences***

Patients not on opioids compared to those who were on opioids prior to surgery:

- were significantly older (median 48 [18 to 79] versus 42 [21 to 63]; p=0.001)
- were significantly older when the first symptoms appeared (median 43 [9 to 77] versus 35 [8 to 59] years; p=0.004)
- had significantly fewer hospitalisations (median 3 [0 to 42] versus 10 [1 to 30]; p=0.001)
- had a significantly shorter duration of symptoms (2 [0 to 40.5] versus 5.9 [0.1 to 22.1]; p=0.038)
- significantly more patients in the opioid compared to the non-opioid group underwent one or more types of total pancreatectomy (21 [46%] versus 19 [14%]; p=0.0002).[134]
  Level 3

►***Pain***

There was a significant difference in the non-opioid and opioid groups on the visual analogue scale (VAS) score preoperatively (median 7 [0 to 10] versus 9 [7 to 10]; p=0.001)and at 3 months (median 2 [0 to 7] versus 3 [0 to 9]; p=0.030). There were no significant differences at 12 (no data) or 24 months (no pain 57 versus 49%; not significant).[134]
Level 3

►***Complications***

Patients on opioids experienced a significantly greater number of haemorrhages and early reoperation [134]. See Table 3-4below.
Level 3

Table 3-4. Summary of results.

	Patients without opioid use n=66	Patients with opioid use n=46	p value
Patients with complications	34	27	0.56
Deaths	1	4	0.15
Pulmonary complications	8	12	0.079
Cardiovascular	6	3	0.73

complications			
Gastrointestinal fistula	12	10	0.63
Abscess/collection	6	8	0.24
Delayed gastric emptying	4	2	0.99
Haemorrhage	2	8	0.015
Early reoperation	3	11	0.003
Other complications	6	2	0.46
Hospital stay	20 (19 to 38)	24 (23 to 47)	0.34

Surgery versus endoscopy

One RCT reported that surgery was more effective than endoscopic treatment with respect to pain control, physical health and the number of procedures required. The mean difference between surgery and endoscopic interventions (adjusting for baseline differences) was 24 points out of 100 on the Izbicki pain score, representing no pain (surgery) or daily pain (endoscopic interventions) or taking no sick leave for pain (surgery) or being permanently unable to work (endoscopic interventions) [130]. The results are summarised in Table 3-5below.

Level 1++

Table 3-5. Summary of results.

	Endoscopy N=19	Surgery N=20	Endoscopic versus Surgical (95%CI)	p value
Izbicki pain score (0 to 100, 100 severe pain)	51±23	25±15	24 (11 to 36)*	<0.001
Pain relief – no. (%)	6 (32%)	15 (75%)	-43 (-72 to -15)**	0.007
Technical success	10 (53%)	20 (100%)	-47 (-70 to -25)**	<0.001
Complications no. (%) **Major** **Minor**	11 (58) 0 11 (58)	7 (35) 1 (5) 6 (30)	23 (-8 to 53)**	0.15
Death no. (%)	1 (5)	0	5 (-5 to 15)**	0.49
Hospital stay – median no. days (range)	8 (0 to 128)	11 (5 to 59)	-3 (-9 to 4)***	0.13
Procedures – median no. (range)	8 (1 to 21)	3 (1 to 9)	5 (2 to 8)***	<0.001
SF-36 quality of				

life				
Physical	38±9	47±7	-8 (-13 to -3)*	0.003
Mental	40±9	45±9	-3 (-8 to 1)*	0.15
Exocrine function				
Insufficiency persisted no.	11	13	RR0.69; 0.54 to 1.47	0.65
Insufficiency developed no.	6	1	RR6.32; 0.84 to 47.69	0.07
Insufficiency resolved no.	1	3	RR0.35; 0.04 to 3.09	0.35
Sufficiency persisted no.	0	3	RR0.15; 0.01 to 3.72	0.2
Endocrine function				
Insufficiency persisted no.	3	4	RR0.79; 0.20 to 3.07	0.73
Insufficiency developed no.	3	1	RR3.16; 0.36 to 27.78	0.30
Insufficiency resolved no.	1	0	RR3.15; 0.14 to 71.88	0.47
Sufficiency persisted no.	11	15	RR0.77; 0.49 to 1.22	0.27

1 No. = number
2 * Mean difference after analysis of covariance with adjustment for baseline values
3 ** Absolute difference between the percentages
4 *** Difference between the medians

Similarly, the study by Dite also reported a significant improvement in pain and increase in body weight associated with surgery compared with endoscopic procedures. The results are summarized in Table 3-6below.

Level 1+

Table 3-6. Summary of results.

	Total group N=140			Randomised group N=72		
	Endoscopic n=64 (%)	**Surgery n=76 (%)**	**RR; 95%CI;p**	**Endoscopic n=36 (%)**	**Surgery n=36 (%)**	**RR; 95%CI; P value**
Mortality	0	0	-	0	0	-
Technical Success	62/64 (97)	-	-	-	-	-
Complications	5 (8)	6 (8)	0.99; 0.32 to 3.09; p=0.99	NR	NR	NR
Abdominal pain: Complete absence	9/64 (14)	28/76 (37)	0.38; 0.19 to 0.75; p=0.005	5/36 (14)	12/36 (33)	0.42; 0.16 to 1.06; p=0.07
Partial relief	33/64 (52)	37/76 (49%)	1.06; 0.76 to 1.47; p=0.73	17/36 (47)	19/36 (53)	0.89; 0.54 to 1.42; p=0.64
No success	22/64 (34)	11/76 (14)	2.38; 1.25 to 4.52; p=0.008	14/36 (39)	5/36 (14)	2.80; 1.13 to 6.95; p=0.03
Body weight: Increase	17/64 (27)	39/76 (51)	0.52; 0.33 to 0.82; p=0.05	10/36 (28)	17/36 (47)	0.59; 0.31 to 1.10; p=0.10
Unchanged	15/64 (23)	15/76 (20)	1.19; 0.63 to 2.24; p=0.60	9/36 (33)	9/36 (33)	1.0; 0.45 to 2.23; p=1.0
Decrease	32/64 (50)	22/76 (29)	1.73; 1.12 to 2.65;	17/36 (47)	10/36 (28)	1.70; 0.91 to 3.19;

			p=0.01			p=0.10
Diabetes mellitus	23/64 (36)	33/76 (43)	0.83; 0.55 to 1.25; p=0.37	12/36 (33)	14/36 (39)	0.86; 0.46 to 1.59; p=0.62

NR = not reported

Complications

►***Endoscopic procedures***

Two bleeding episodes, two cases of acute pancreatitis and one pancreatic abscess [131] were reported.

Level 1+

►***Surgery***

Two cases of acute pancreatitis, two fistulas, one case of ileus and one case of anastomotic leakage. One patient underwent repeat surgery due to ileus and one patients for anastomotic leakage [131].

Level 1+

3.3.4 Health economic methodological introduction

No cost-effectiveness analysis was identified that assessed the treatment and the timing for treating people with alcohol-related chronic pancreatitis using coeliac access block, splanchnicectomy, endoscopic interventional procedures, or surgery.

In current medical practice in England and Wales, surgical and endoscopic interventions are available for patients with chronic pancreatitis and a dilated pancreatic duct. The clinical literature review included two RCTs comparing endoscopic and surgical interventions in this population of patients[130,131]. The findings of both RCTs showed that surgical drainage of the pancreatic duct was more effective than endoscopic drainage.

Surgical and endoscopic drainage of the pancreatic duct are interventions associated with extensive resource use and cost, and there is a lack of published health economic evidence to support the use of one or the other. For these reasons, we undertook our own economic evaluation comparing these two interventions (see A.4 for the full analysis).

3.3.5 Health economic evidence statements

The objective of the economic analysis undertaken was to assess the cost-effectiveness of the surgical drainage of the pancreatic duct compared to the endoscopic drainage, for patients with chronic pancreatitis and an obstructed pancreatic duct in England and Wales.

This economic analysis was conducted mainly based on the Cahen 2007 study[130], from an England and Wales NHS perspective, over a 24-month time horizon for the base-case analysis (median follow-up time in the Cahen trial). A lifetime horizon was used in the

sensitivity analysis. The health outcome considered was Quality-Adjusted Life Year (QALY). An annual discount rate of 3.5% was applied to both costs and health outcomes incurred after one year.

In the Cahen study[130], the EQ-5D questionnaire was completed by participants (unpublished). Data were collected for each arm at baseline, six weeks, three months, six months, 12 months, 18 months, and 24 months. The patient-level EQ-5D data from the trial was obtained and utility scores generated for both arms at every follow-up point using the UK tariff. As the baseline utility scores differed slightly between arms, it was controlled for utility score at baseline by applying linear regression. The utility scores were used to calculate QALYs (utility score * time-period) for the 24-month duration of the trial for the base-case analysis, and a lifetime horizon in sensitivity analyses. For the lifetime horizon, a constant utility score, post trail, was assumed for the endoscopy group (using the value at 24 months). No difference in utility score post-trial between the cohorts and therefore applied the constant utility score of the endoscopy group (value at 24 months) to the surgical cohort was assumed.

Costs considered in this analysis, taken from the Cahen trial[130] for the first 24 months (Cahen trial follow-up), were related to therapeutic procedures (surgical drainage, endoscopic drainage, and lithotripsy sessions), diagnosis procedures, the treatment of complications, the treatment of exocrine insufficiency, and the conversion to surgical drainage for patients in the endoscopic arm in who the treatment failed. After 24-months, the same yearly cost was applied to patients in both the surgery and endoscopy groups, and was extrapolated from the observed resource usage from the Cahen trial.

Cahen 2007[130] and Dite 2003[131] RCTs reported no deaths related to the interventions. No mortality was considered in the base-case analysis. From a review of clinical studies, the mortality related to surgical drainage was estimated to be 1.1%. It was decided to use a mortality rate related to surgery of 1.1% and an upper estimate of 2% in the sensitivity analysis. These mortality rates were applied to patients in the surgical group and to patients who converted to surgery in the endoscopic group, and were applied on the Cahen within-trial time horizon (24 months) and on a lifetime horizon.

Sensitivity analyses were performed to assess the robustness of the results to plausible variations in the model parameters. Five one-way sensitivity analyses were conducted, varying one parameter at a time from the base case: two were costing differently the diagnostic procedures; two were varying the ratio of patients who convert to surgery after failure of the endoscopic treatment using extreme values from a review of clinical studies; and one varied the length of hospital stay adjusting the amount of in-patient bed-days from the length of hospital stay included in the HRG-code cost to the amount reported by the Cahen study[130]. In addition, two-way sensitivity analyses were performed, concurrently using two extreme varying estimates from a review of clinical studies: the probability of stent-related complication (endoscopic group) and the rate of re-operation (surgical group). Four combinations were assessed. Finally, sensitivity analyses were conducted applying mortality rates to surgical drainage on the Cahen within-trial time horizon (24 months) and on a lifetime horizon.

The economic analysis presents probabilistic results. A probabilistic analysis applies probability distributions for model parameters and presents the empirical distribution of the cost-effectiveness results. The result of the base-case analysis was that surgical drainage of the pancreatic duct dominates endoscopic drainage (it was more effective and less costly – Table 3-7.). The sensitivity analysis showed that the surgical option remains dominant (cost-saving) in a majority of scenarios (Table 3-8 and Table 3-9). The results were most sensitive to the proportion of patients in the endoscopy group who convert to surgical drainage when the endoscopic drainage failed. When patient conversion to surgery was less than 10%, surgical drainage was no longer cost-saving, but it was still highly cost-effective when compared with a threshold of £20,000 per QALY gained (£1,729 per QALY gained when the probability of conversion to surgery was 0% - Table 3-8). The base-case analysis, the analyses considering mortality rates related to surgical drainage, and all other sensitivity analyses showed very high probabilities of cost-effectiveness for surgical drainage compared to endoscopic drainage. The presented results reveal that surgical drainage is highly cost-effective compared to endoscopic drainage.

Table 3-7.

Base-case analysis probabilistic results: Mean costs		
	Endoscopy	**Surgery**
Therapeutic procedures	£5,328	£6,153
Diagnostic procedures	£501	£339
Complications	£197	£284
Exocrine function	£800	£671
Conversion to surgery	£1,243	n/a
Total	**£8,068**	**£7,446**

Table 3-8.

Probabilistic results					
	Cost Difference (surgery-endoscopy)	**Probability of surgery being cost-saving**	**QALY gained (surgery – endoscopy)**	**Incremental Net Monetary Benefit* (surgery - endoscopy)**	**Probability of surgery being cost-effective***
Base-case analysis	-£622	55.6%	0.39	£8,472	99.1%
Sensitivity analyses considering mortality related to surgery					
1.1% mortality related to surgery – 24-month time horizon	-£622	55.6%	0.38	£8,150	99.0%
2% mortality related to surgery – 24-month time horizon	-£622	55.6%	0.36	£7,911	98.7%
1.1% mortality related to surgery – lifetime horizon	-£828	57.7%	0.31	£7,008	97.5%

2% mortality related to surgery – lifetime horizon	-£969	59.4%	0.25	£5,939	95.5%
Other one-way sensitivity analysis					
Diagnostic procedure - 100% MRI	-£622	55.7%	0.39	£8,483	99.3%
Diagnostic procedure - 100% CT-Scan	-£656	56.4%	0.39	£8,454	99.1%
Lower estimate for conversion to surgery post-endoscopy (0%)	£676	40.8%	0.39	£7,142	96.5%
Higher estimate for conversion to surgery post-endoscopy (28%)	-£960	59.5%	0.39	£8,808	99.4%
Length of hospital stay adjustment	-£5	48.0%	0.39	£7,855	98.6%

* Compared with a threshold of £20,000 per QALY gained

Table 3-9.

Two-way sensitivity analysis		**Endoscopic complication rates**	
		Higher (64%)	**Lower (8%)**
Surgical complication rates	**Higher (7.1%)**	-£779* 56.6%** £8,598¥ 99.0%¥¥	-£268 51.1% £8,145 99.1%
	Lower (2.6%)	-£1023 59.0% £8,863 99.3%	-£612 55.1% £8,446 98.9%

* Cost difference (surgery - endoscopy)
** Probability of surgery being cost-saving
¥ Incremental Net Monetary Benefit – £20,000 per QALY gained (surgery - endoscopy)
¥¥ Probability of surgery being cost-effective at £20,000 per QALY gained

A 24-month time horizon was chosen for the base-case analysis as this was the period covered by the Cahen study[130]. It was judged that extrapolating the results of the Cahen trial would involve uncertainty and that the 24-month time horizon adequately captures the difference in economic and health outcomes between the compared interventions (keeping in mind that these treatments are undertaken for pain-control). The Cahen trial was stopped after an interim analysis on the basis of a significant difference in outcomes favouring surgery. This may have resulted in overestimating the health outcomes in favour of surgery.

The sensitivity analysis varying the probability for conversion to surgery in the endoscopy group showed that surgical drainage was no longer cost-saving when patient

conversion to surgery was less than 10%. However, even with a probability of conversion to surgery of 0% surgery was highly cost-effective with a cost of £1,729 per QALY gained.

The sensitivity analysis adjusting the amount of in-patient bed-days from the length of hospital stay included in the HRG-code cost to the amount reported by the Cahen study[130], showed low cost savings for surgery, with the probability that surgery is cost-saving being 48%. However. the probability that surgery is cost-effectiveness for this analysis was 98.6%. The Cahen study[130] was conducted in the Netherlands, a country with a healthcare system and with practices in this area that may be different to the UK NHS. Therefore the base-case analysis using the HRG-code length of hospital stay is perhaps more relevant for estimating the cost impact on the UK NHS.

The sensitivity analysis applying mortality rates of 1.1% and 2% to surgical drainage showed cost-saving results with very high probabilities of cost-effectiveness. Furthermore, the probability that surgery is cost-effectiveness was very high across all analyses, varying from 95.5% to 99.4%.

The medians were used to estimate means for some resource use outcomes, because they were the best available estimates as reported by Cahen 2007[5]. In health economic assessments, the mean is the most informative measure for costing resource use, and provide information about the total cost that will be incurred by treating all patients, which is needed as the basis for healthcare policy decisions. The median in contrast describe a 'typical' cost for an individual[135]. The most costly interventions (surgical and endoscopic therapeutic procedures, and lithotripsy sessions) were costed using median estimates. Although, the mean estimates by Dite 2003[131] for numbers of therapeutic procedures seem to be in agreement with Cahen 2007[130] medians. Moreover, to be safe, we used conservative assumptions not favouring surgical drainage when costing lithotripsy sessions.

Finally, the results of the present study cannot be extrapolated to all patients with ductal obstruction due to chronic pancreatitis because patients with an inflammatory mass were excluded from the Cahen trial[130].

3.3.6 From evidence to recommendations

The GDG recognised that it was not within their scope to determine the safety or efficacy of a specific surgical procedure for pain. Instead, they searched for evidence that would help determine whether there is benefit for referral for intervention rather than conservative management and when this should be done (either 'early', when the pain commences, or 'late' after conventional escalation of treatment along the analgesic ladder until this fails). More specifically, they attempted to determine whether there was evidence for preferring coeliac axis block over splanchnicectomy, if either is considered,

[5] Number of surgical and endoscopic therapeutic interventions; number of diagnostic interventions; total length of hospital stay; number of lithotripsy sessions.

and whether endoscopic procedures are better than surgery, if either of these is considered.

The GDG noted that without intervention, a proportion of patients will become relatively pain-free due to the natural history of the disease. However, there was concern that the proportion of patients who become pain-free without intervention may be over-estimated.

The group discussed the likelihood that most patients with pain related to chronic pancreatitis are not referred for consideration for surgical or endoscopic procedures. A critical step in determining the optimal treatment is to determine whether the patient has large (obstructive) or small (non-obstructive) duct disease. It was agreed that this disease sub-stratification should be done as part of the routine assessment of these patients. The recommendations reflect this consideration by encouraging referral to a specialist centre for consideration of multidisciplinary assessment.

The evidence comparing splanchnicectomy to coeliac axis block was of poor quality and consisted of two case-control studies with small sample sizes. Due to the very limited evidence base, the GDG felt that they were unable to make any recommendations that would favour one intervention over the other.

There were two moderate-quality trials comparing surgery with conservative management. The GDG did not think these provide definitive information, but support the recommendation that patients should be referred for multidisciplinary assessment and consideration of surgery.

The literature comparing early to late surgery (before versus after long term opioid use) indicated that it was better to operate early thereby avoiding the possible problem of opioid dependence.

With regard to large (obstructive) duct disease, there were two RCTs comparing endoscopic against surgical intervention; one of moderate quality and one of high quality. The high-quality study was terminated early due to significantly improved outcomes associated with surgical intervention. This trial suggests that surgical treatment is optimal in this population. The GDG was, however, reluctant to recommend surgical therapy as the only option in these patients. There is a small, but definite mortality and some patients may do well with endoscopic therapy. On the other hand, endoscopic drainage involves more interventions than surgical drainage (median of 5 versus median of 1 according to the high quality study – Cahen 2007[130]). The cost-effectiveness analysis undertaken comparing surgical and endoscopic drainages in patients with large duct (obstructive) chronic pancreatitis showed that surgical drainage is highly cost-effective compared to endoscopic drainage. It was agreed that patients with large duct (obstructive) chronic pancreatitis should be offered surgery given that current evidence suggests better outcomes with surgery compared to endoscopy.

With regard to pain from small duct disease, there is considerable debate over the optimum management. Surgery was considered more controversial than in the large duct disease population. In addition, the GDG was unable to determine from the evidence whether coeliac axis block or splanchnicectomy was better for pain relief in this population. The group did agreed on consensus, however, that patients with severe symptoms should be referred to a centre where these procedures are available and that if appropriate they should be offered interventional therapy.

3.3.7 Recommendations

R27 Refer people with pain from chronic alcohol-related pancreatitis to a specialist centre for multidisciplinary assessment.

R28 Offer surgery, in preference to endoscopy, to people with pain from large-duct (obstructive) chronic pancreatitis.

R29 Offer people with poorly controlled pain from small-duct (non-obstructive) chronic alcohol-related pancreatitis coeliac axis block, splanchnicectomy or surgery.

3.4 Prophylactic antibiotic treatment for acute pancreatitis

3.4.1 Clinical Introduction

Acute alcohol-related pancreatitis can present as a relatively mild syndrome which resolves spontaneously or as a severe illness with a high mortality. Acute necrotizing pancreatitis can be complicated by infection of the necrotic pancreatic tissue and this infection has an impact on morbidity and mortality. These infections are often bacterial. Whilst antibiotic treatment for acute infections is not debated amongst clinicians, the role of prophylactic antibiotics is; randomised trials of prophylactic antibiotics have been performed since the 1970s. In spite of this, there is variation in practice across the UK, presumably because of conflicting trial results.

The GDG sought to provide recommendations for the use of antibiotics in this condition and thus searched the literature to address the following clinical question:

In patients with acute alcohol-related pancreatitis, what is the safety and efficacy of prophylactic antibiotics versus placebo?

3.4.2 Clinical methodological introduction

For the comparison antibiotics versus placebo/no treatment, three RCTs on patients with acute mild pancreatitis were identified [136]; [137]; [138]. These studies were performed before CT imaging was available. See table below for the study characteristics.
Level 1+

For patients with acute severe pancreatitis, seven RCTs were identified [139] [140] [141] [142] [143] [144]. Only papers that used CT to confirm the diagnosis of pancreatitis were included. One open label RCT was excluded due to study limitations [145].
Level 1+

3.4.3 CLINICAL EVIDENCE STATEMENTS

►*Mild pancreatitis*

A summary of the results is presented in Table 3-10below. There were no significant differences between the patients treated with antibiotics and those without in terms of mortality, length of hospitalisation, duration of elevated serum amylase or fever [136]; [137]; [138].
Level 1+

One study reported that a significantly greater proportion of patients treated with antibiotics experienced recurrent pancreatitis [136].
Level 1+

Table 3-10. Summary of results.

	Antibiotic	No antibiotic	P value
Mortality			
HOWES[138]	0	0	ns
FINCH[136]	1	0	ns
CRAIG[137]	0	0	ns
Hospitalisation (days)			
HOWES[138]	9	12	ns
FINCH[136]	10	11	ns
CRAIG[137]	NR	NR	-
Amylase elevation (days)*			
HOWES[138]			
FINCH[136]	2	2	ns
CRAIG[137]	5	4.5	ns
	6	5	ns
Fever (days)**			
HOWES[138]	3	3	ns
FINCH[136]	7	6	ns
CRAIG[137]	3	3	ns
Recurrent Pancreatitis			

HOWES[138]	NR	NR	-
FINCH[136]	6/31 (19.4%)	2/27 (7.4%)	P<0.05
CRAIG[137]	NR	NR	-

*Howes and Craig – mean number of days with findings; Finch – Normal serum amylase achieved by day. Elevated serum amylase > 160 UI/dl

** Howes and Craig – mean number of days with findings; Finch – Mean day at which patient afebrile

►***Complications***

There were no significant differences in the number of serious complications reported in relation to antibiotic use. [136] [137] [138]

Level 1+

►***Severe necrotising pancreatitis***

Table 3-11below summarises the results of the meta-analysis (all studies) for the RCTs on patients with severe acute pancreatitis. Refer to figures Figure 3-1, Figure 3-2, Figure 3-3, Figure 3-4, and Figure 3-5 for forest plots from the meta-analysis.

Table 3-11. Summary of results.

	Overall	Carbapenem	Other antibiotics
Pancreatic infection (Carbapenem N=2; Other N=4)	0.97 (0.69 to 1.37); p=0.87	1.06 (0.53 to 2.16); p=0.86	0.94 (0.63 to 1.38)
Heterogeneity	0%; p=0.82	15%; p=0.86	0%; p=0.81
Mortality (Carbapenem N=2; Other N=4)	0.54 (0.33 to 0.88); p=0.01	0.94 (0.47 to 1.90) P=0.87	0.32 (0.16 to 0.67); p=0.002
Heterogeneity	16%; p=0.31	0%; p=0.47	0%; p=0.66
Non-pancreatic Infection (Carbapenem N=2; Other N=3)	0.60 (0.44 to 0.82); p=0.001	0.51 (0.34 to 0.78) P=0.002	0.74 (0.46 to 1.17); p=0.20
	0%; p=0.42	63%; p=0.10	0%; p=0.88
Surgical intervention (Carbapenem N=2; Other N=3)	0.98 (0.71 to 1.35); p=0.89	1.07 (0.65 to 1.75); p=0.79	0.91 (0.59 to 1.40); p=0.67
	15%; p=0.89	0%; p=0.44	50%; p=0.67
Length of stay (Other N=1)	-10.60 (-27.93 to 6.73); p=0.23		

Figure 3-1. Antibiotics versus placebo, outcome: pancreatic infection.

Figure 3-2. Antibiotics versus placebo, outcome: mortality.

Figure 3-3. Antibiotics versus placebo, outcome: Non-pancreatic infection.

Figure 3-4. Antibiotics versus placebo, outcome: Surgical intervention

Figure 3-5. Antibiotics versus placebo, outcome: Length of stay

Summary of findings

►***Antibiotics versus placebo***

Overall, prophylactic antibiotics compared to placebo were associated with a significant reduction in:

- Mortality
- Non-pancreatic infection

Level 1+

There were no significant differences between prophylactic antibiotics and placebo for:

- Pancreatic infection
- Surgical intervention
- Length of stay

Level 1+

►***Carbapenem versus placebo***

Carbapenem compared with placebo was associated with a significant reduction in:

- non-pancreatic infection (moderate to high heterogeneity)

Level 1+

There are no significant differences between carbapenem and placebo for:

- pancreatic infection
- mortality
- surgical intervention.

No data was reported for length of stay.

Level 1+

► ***'Other antibiotics' versus placebo***

'Other antibiotics' compared to placebo were associated with a significant reduction in:

- mortality.

Level 1+

There was no significant difference between 'other antibiotics' and placebo for:

- pancreatic infection
- non-pancreatic infection
- surgical intervention
- length of stay.

Level 1+

3.4.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis was identified assessing the cost-effectiveness of prophylactic antibiotics for patients with acute alcohol-related pancreatitis. Costs and resource use information associated with the use of prophylactic antibiotics in patients with acute alcohol-related pancreatitis were presented to the GDG.

3.4.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

The main components of resource use associated with prophylactic antibiotic therapy for patients with acute alcohol-related pancreatitis are the treatment itself and the hospital stay. The treatment cost is high, varying from £200 to nearly £2000 when costing therapies used in clinical trials included from the clinical review[117]. For the hospitalisation cost, the clinical review showed that the length of hospital stay was not significantly reduced using prophylactic antibiotics either in patients with mild acute pancreatitis or in patients with severe acute pancreatitis.

3.4.6 *FROM EVIDENCE TO RECOMMENDATIONS*

The evidence for this clinical question is reported separately for mild and severe acute pancreatitis. There was variability in the definition of severe pancreatitis which makes it difficult to issue clear guidance based on the available evidence. In addition, the trials used different antibiotics for different durations.

►***Mild acute pancreatitis***

The GDG considered the evidence for antibiotic treatment in mild acute alcohol-related pancreatitis. It was noted that the trials were over 30 years old and were performed before the advent of CT as a diagnostic and prognostic tool. All the trials used a short course of ampicillin. The clinical evidence did not support the use of antibiotics on the basis of the chosen outcomes.

Given that the evidence for antibiotics in mild pancreatitis was based on a single drug (ampicillin) the GDG found it difficult to make a recommendation based solely on the clinical evidence review. There was no health economic evidence available to influence the recommendation.

The GDG therefore agreed, by consensus, that antibiotics should not be given to patients with mild acute pancreatitis as no positive evidence for their use had been found. Patients should to be monitored to ensure that their condition does not progress from a mild to severe state, when the question of antibiotic use would be raised again.

►***Severe acute pancreatitis***

The GDG considered the evidence for use of prophylactic antibiotics in severe acute pancreatitis. There was variability in the definition of severe pancreatitis and the trials used different antibiotics for different treatment durations. While a carbapenem was found to reduce non-pancreatic infections, it was 'other antibiotics' that were found to reduce mortality in the meta-analysis.

At present there is no nationwide or European clinical consensus on this topic and the evidence reviewed was variable and is interpreted differently between centres in the UK.

3.4.7 *RECOMMENDATIONS*

R30 Do not give prophylactic antibiotics to people with mild acute alcohol-related pancreatitis.

R31 Offer prophylactic antibiotics to people with severe acute alcohol-related pancreatitis.

3.5 NUTRITIONAL SUPPORT FOR ACUTE ALCOHOL-RELATED PANCREATITIS

3.5.1 CLINICAL INTRODUCTION

Supportive care is the mainstay of treatment for acute pancreatitis. The timing and delivery of nutritional therapy is an important component of this care. There are three broad treatment options; withhold feeding, enteral nutrition (either oral or tube feeding) and parenteral nutrition. Each option has historically had periods of clinical favour. The supporters of withholding enteral feeding (or feeding nasojejunally) suggest that resting the pancreas avoids exocrine secretion and further pancreatic injury. Supporters of enteral feeding highlight the importance of maintaining nutritional intake and intestinal integrity, reducing bacterial translocation and thereby limiting the systemic inflammatory immune response.

Oral nutritional intake in pancreatitis, particularly if severe, is often limited by nausea so enteral feeding often implies either nasogastric or nasojejunal feeding. Parenteral feeding is generally given as total parenteral nutrition. Many trials have attempted to answer the question of which form of feeding is superior and results have been conflicting. By looking at all the evidence to date with regard to a wide variety of outcome measures from mortality to sepsis and multi-organ failure, the GDG aimed to provide guidance on the most clinical and cost-effective modality. The data are based on studies in patients with acute pancreatitis irrespective of aetiology.

The clinical question searched was:

'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?'

In patients with acute alcohol-related pancreatitis, what is the safety and efficacy of:

a) *nutritional supplementation versus no supplementation*
b) *early (first 48 hours) versus late supplementation*
c) *enteral versus parenteral nutrition*
d) *nasojejunal versus nasogastric feeding*

3.5.2 CLINICAL METHODOLOGICAL INTRODUCTION

Studies were included that reported on the safety and efficacy of nutritional supplementation versus no supplementation; early (first 48hours) versus late supplementation; enteral versus parenteral nutrition or nasojejunal versus nasogastric nutrition in patients with acute alcohol related pancreatitis. Outcomes of interest were mortality, length of hospitalisation, systemic inflammatory response syndrome (SIRS),

multiple organ failure (MOF), operative intervention, infection and local complications (such as abscesses).

Fifteen studies were included in the review; thirteen RCTs [124,146-157] and two SRs [158,159] The results of the studies included in the SRs were reported separately if they included further outcomes of interest not covered by the SRs.

Outcomes reported were mortality, infection, length of stay, MOF, SIRS, pancreatic complications and operative interventions.

The studies were reported under the following categories:

1. nutritional supplementation versus no supplementation (n=4)
2. enteral versus parenteral nutrition (n=9)
3. nasojejunal versus nasogastric (n=3)

No studies were found that directly compared early (first 48 hours) versus late supplementation. A more detailed summary of the included studies can be seen below.

Limitations

- The number of patients with alcohol related pancreatitis ranged from 11% [157] to 81% [147] across the studies, and was not reported in one of the SRs [158].
- A number of the included studies were underpowered for outcomes of interest [151,152,154]
- One of the NJ versus NG studies [152] included patients with both mild and severe acute pancreatitis rather than severe acute pancreatitis which was the clinically relevant population selected

Summary table of included studies

	Population	Intervention	Comparison
ECKERWALL 2007[148]	Patients with clinical signs of mild acute pancreatitis, pancreas amylase ≥ 3 times above normal, onset of abdominal pain within 48h, acute physiological and chronic health evaluation score (APACHE) II <8 and C-reactive protein (CRP) <150mg/L. N=60 (one drop out) Alcohol related: oral feeding group 3/30; fasting group 5/30; total 13%	Fasting (+ iv fluids) - oral fluids and diet reintroduced in a traditional step-wise manner as tolerated. N=30	Immediate oral feeding (+ iv fluids when needed) N=30 (1 dropped out n=29 completed)
SAX 1987[155]	Patients with acute abdominal pain, clinical findings of abdominal tenderness in the left upper quadrant, nausea, or vomiting; a history of alcohol	TPN + conventional therapy (see comparison) started within	Conventional therapy (iv fluids, analgesics, antacids,

	abuse or gallbladder disease; and laboratory findings of an increased amylase level +/- radiographic confirmation of pancreatic calcifications consistent with chronic pancreatitis. N=54 Alcohol related: early TPN 86%; no nutrition 76%	24 hrs of admission. n=29	nasogastric insertion) n=26
XIAN-LI 2004[157]	Patients with severe acute pancreatitis (SAP) diagnosed by clinical evaluations, clinical biochemistry and CT scanning of the pancreas, according to the universal standard for SAP diagnosis in China. N=64 Alcohol related: 7/64 (11%)	Group I: traditional conservative therapy (iv fluids, electrolyte replacement, starvation treatment, NG decompression, analgesics, pancreatic exocrine secretion suppression, prophylactic antibiotics and necessary infusion of albumin or fresh plasma) n=23	Group II: traditional conservative therapy + TPN (iso-caloric + iso-nitrogenous) n=21 Group III: traditional conservative therapy + TPN + additional glutamine dipeptide-supplementation n=20
PETROV 2008 [158]	n=9 studies included patients with severe acute pancreatitis. n=6 studies included patients with mild and severe acute pancreatitis. N=15 studies in total N= 617 patients Alcohol related: not reported	1) enteral nutrition (n=11 studies) 2) parenteral nutrition (n=3 studies) 3) enteral nutrition (n=1 study)	1) parenteral nutrition 2) no supplementary nutrition 3) no supplementary nutrition
ECKERWALL 2006[160]	Patients with a clinical diagnosis of acute pancreatitis (abdominal pain, amylase 3 or more time the	Parental N=26	Enteral N=24

	upper limit of normal, onset of abdominal pain within 48 hrs, APACHE II 8 or more and/or CRP of 150 mg/L or more and/or pancreatic liquid shown on CT) N=50 Alcohol related:14%		
ABOU-ASSI 2002[156]	Patients with acute pancreatitis who were in need of nutritional support, with acute abdominal pain, 3-fold elevation of serum pancreatic enzymes, amylase, lipase. N=53 Alcohol related: 62%	Total parenteral nutrition (TPN) n=27	Total enteral nutrition (TEN) –via NJ tube n=26
McCLAVE 1997[154]	Patients with acute pancreatitis or an acute flare of chronic pancreatitis N=32 Alcohol related: TEN group: 75% (±11.2); TPN group: 62.5 % (±12.5)	Total parenteral nutrition (TPN) n=16	Total enteral nutrition (TEN) n=16
PETROV 2006[149]	Patients with severe acute pancreatitis within 72 hrs of onset. Diagnosis was based on clinical and biochemical presentation N=69 Alcohol related: enteral: 11/35; parenteral: 15/34; total 38%	Parental N=34	Enteral N=35
GUPTA 2006[124]	Patients with acute pancreatitis (defined as abdominal pain and serum amylase concentration of 1000 U/I or more). The diagnosis of predicted severe acute pancreatitis was established by the presence of APACHE II of 6 or more N=17 Alcohol related: enteral 1/8; parenteral 5/9; total 35%	Parental N=9	Enteral N=8 Feeding through NJ tube
KALFARENTZOS 1997[153]	Patients with acute severe pancreatitis (3 or more criteria according to the Imrie classification or APACHE II score of 8 or more, C-reactive protein >	Parental N=20	Enteral N=18 Through

	120 mg/l within 48 hrs of admission, and grade D or E by CT according to Balthazar criteria) N=38 Alcohol related: enteral 3/18; parenteral 2/20; total 13%		nasoenteric feeding tube
OLAAH 2002[147]	Patients with acute pancreatitis admitted to the surgical ward (clinical symptoms and laboratory signs of pancreatitis (amylase > 200 U/L) N=89 Alcohol related: enteral 33/41; parenteral 39/48; total 81%	Parental N=48	Enteral N=41 NJ tube
WINDSOR 1998[146]	Patients with acute pancreatitis with a serum amylase of > 1000 IU N=34 Alcohol related: enteral 2/16; parenteral 2/18; total 12%	Parental nutrition N=18	Enteral nutrition N=16
PETROV 2008[158]	RCTs of nasogastric versus nasojejunal feeding in patients with severe acute pancreatitis. N=2 studies in meta-analysis N=79 patients Alcohol related: total in NG group 10/43 (23%)	Enteral nutrition via nasogastric feeding N=43	Enteral nutrition via nasojejunal feeding N=36
KUMAR 2006[151]	Patients with severe acute pancreatitis. The severity was defined according to Atlanta criteria- presence of organ failure and acute physiology and chronic health evaluation score of ≥8 or CT severity score ≥7. N=31 Alcohol related: NJ group 4/14; NG group 4/16; total 27%	Nasojejunal (NJ) feeding N=14 -all patients achieved the goal of 1800kcal within 7 days from start of feeding (4 patients were supplemented by parenteral nutrition during feeding)	Nasogastric (NG) feeding N=16 -all patients achieved the goal of 1800kcal within 7 days from start of feeding (6 patients were supplemented by parenteral nutrition during feeding)
EATOCK 2005[152]	Patients with both a clinical and biochemical presentation of acute pancreatitis (abdominal pain +	Nasogastric feeding	Nasojejunal feeding

	serum amylase at least 3 times the upper limit of the reference range), and objective evidence of disease severity (Glasgow prognostic score 3 or more, or a APACHE II score 6 or more or a CRP level >150 mg/L) N=49 Alcohol related: total 24.5%	N=27 77.8% of target calories were delivered beyond 60 hrs	N=22 76.1% of target calories were delivered beyond 60 hrs.

3.5.3 CLINICAL EVIDENCE STATEMENTS

Nutritional support versus no nutritional support

►***Mortality***

The systematic review [158] reported on the difference in mortality in those treated with:

a) parenteral nutrition versus none (3 RCTs):

- Parenteral nutrition resulted in a statistically significant 64% reduction in risk. Parenteral group 4/56; no nutrition group 13/57. RR0.36 (95% CI 0.13, 0.97) p=0.04 (no heterogeneity)

b) enteral nutrition versus None (1 RCT):

- Enteral nutrition resulted in a 78% reduction in risk. RR (95% CI): 0.22 (0.07-0.70) p= 0.01

Level 1+

One other study reported on the difference in mortality between those treated with immediate oral refeeding (+ iv fluids when needed) versus fasting [148]:

- No deaths in either group.

Level 1+

►***Infection***

The systematic review [158] reported on the difference in infectious complications in those treated with:

a) parenteral nutrition versus none (3 RCTs)

- Parenteral nutrition resulted in a statistically non-significant increase of 36% in the risk of infectious complications. Parenteral group 8/49; no nutrition group 8/49; risk ratio 1.36 (95% CI 0.18-10.40) p=0.77 (moderate heterogeneity between study results).

b) enteral nutrition versus none (1 RCT):

- Risk reduced non-significantly by 44% with the use of enteral nutrition over no nutrition. RR (95% CI): 0.56 (0.07-4.32) p=0.58. This difference was probably non-significant due to the small sample size.

Level 1+

►***Length of stay (LOS)***

Three studies reported on the differences in length of stay between those treated with nutritional support versus no nutritional support. See Table 3-12 for a summary of results.

Table 3-12. Summary of results.

	LOS (days)			
	Nutrition support	No nutrition support	Mean Difference (95% CI)	P value
ECKERWALL 2007[148] (mean) - - immediate oral feeding versus fasting	4	6	-	0.047
XIAN-LI 2004[157] (mean ± SD) - TPN versus conservative therapy	28.6 ± 6.90	39.1 ± 10.60	-10.50 (-15.74, -5.26)	<0.05
XIAN-LI 2004[157] (mean ± SD) - TPN + additional glutamine dipeptide-supplementation versus conservative therapy	25.3 ± 7.60	39.1 ± 10.60	-13.80 (-19.26, -8.34)	<0.01
SAX 1987[155] (mean) - TPN versus conservative therapy	16	10	-	<0.04

Level 1+

►***Multi-organ failure (MOF)***

One study reported on MOF in those treated with nutritional support versus no nutritional support, and showed no obvious benefit. See Table 3-13 for a summary of results.

Table 3-13. Summary of results.

	MOF		
	Nutrition support	No nutrition support	RR (95% CI)
XIAN-LI 2004[157] (mean ± SD) - TPN versus conservative therapy	2/21	4/23	0.55 (0.11, 2.69)
XIAN-LI 2004[157] (mean ± SD) - TPN + additional glutamine dipeptide-supplementation versus conservative therapy	0/20	4/23	0.13 (0.01, 2.22)

Level 1+

►***Systemic inflammatory response syndrome (SIRS) (CRP, leukocytes)***

One study reported on two markers of SIRS, CRP and leukocytes in those treated with immediate oral feeding versus fasting, and showed no obvious benefit. See Table 3-14 and Table 3-15 for a summary of results.

Table 3-14. a) CRP

	CRP (Mg/L)		
	Nutrition support	No nutrition support	P value
ECKERWALL 2007[148] mean (range)	61 (26-127)	81 (45-139)	NS

Table 3-15. b) leukocytes

	Leukocytes (10 9/L)		
	Nutrition support	No nutrition support	P value
ECKERWALL 2007[148] mean (range)	6.6 (6.3-10.2)	7.7 (6.4-10.8)	NS

Level 1+

►***Pancreatic complications***

One study [148] reported on this outcome for nutritional support versus no nutritional support and reported no complications such as necrosis, abscess or pseudocysts in either group.

Level 1+

►***Operative interventions***

One study [148] reported on this outcome for nutritional support versus no nutritional support and reported no significant difference between groups concerning the number of interventions performed during hospital stay (cholecystectomy and endoscopic retrograde cholangiopancreatography)

- Fasting 7/30 versus oral refeeding 6/29, p>0.30; RR 1.13 (95% CI 0.43, 2.96)

Level 1+

Enteral versus parenteral

►***Mortality***

The SR [158] reported on the difference between in-hospital mortality in those treated with enteral versus parenteral nutrition (n=9 RCTs)

- Enteral nutrition resulted in a non-significant 40% reduction in risk. Enteral group 16/191; parenteral group 34/213; risk ratio 0.60 (95% CI 0.32, 1.14) p=0.12. Heterogeneity explained by random variation.
  Level 1+

►***Infection***

The SR [158] reported on the difference in infectious complications seen between those treated with enteral versus parenteral nutrition (n=10 RCTs).

- Enteral nutrition resulted in a significant 59% reduction in risk compared to parenteral nutrition. Enteral group 33/204; parenteral group 89/226; RR0.41 (95% CI 0.30, 0.57) P<0.00001. Heterogeneity explained by random variation. **Level 1+**

►***Length of stay***

Six of the studies reported on the difference in length of stay between those treated with enteral versus parenteral nutrition. A meta-analysis was performed on two of the studies [154,156] where adequate data were available. However due to 80% heterogeneity between the studies the results were reported separately. Overall, no difference was seen between the groups. See Table 3-16 for a summary of results.

Table 3-16. Summary of results.

	Length of stay (days)			
	Enteral (EN)	Parenteral (PN)	Mean difference (95% CI)	P value
McCLAVE 1997[154] mean ± SD	9.7 ± 1.3	11.9 ± 2.6	-2.20 (-3.62, -0.78)	-
ABOU-ASSI 2002[156] mean ± SD	14.2 ± 1.9	18.4 ± 1.9	-4.20 (-5.22, -3.18)	-
ECKERWALL 2006[150] Median (range)	7 (6-14)	9 (7-14)	-	0.19
GUPTA 2003[124] Median (range)	7 (4-14)	10 (7-26)	-	0.05
KALFARENTZOS 1997[153] Median (range)	40 (25-93)	39 (22-73)	-	-
WINDSOR 1998[146] Median (range)	12.5 (9.5-14)	15 (11-28)	-	NS

Level 1+

►***Multi-organ failure (MOF)***

Four studies reported on the difference in MOF between those treated with enteral versus parenteral nutrition. The results varied across the studies. However, most showed a non-significant difference across the groups favouring enteral feeding. See Table 3-17 for a summary of results.

Table 3-17. Summary of results.

	MOF			
	Enteral (EN)	Parenteral (PN)	RR (95% CI)	P value

ECKERWALL 2006 (%)[150]	1/24 (4)	1/26 (4)	1.08 (0.07,16.38)	-
PETROV 2006 (%)[149]	7/35 (20)	17/34 (50)	0.40 (0.19, 0.84)	0.05
OLAAH 2002 (%)[147]	2/41 (5)	5/48 (10)	0.47 (0.10, 2.29)	NS
-severe pancreatitis subgroup	2/7 (29)	5/10 (50)	0.57 (0.15, 2.15)	NS
WINDSOR 1998 (%)[146]	0/16 (0)	5/18 (28)	0.10 (0.01, 1.70)	-

Level 1+

Nasogastric (NG) versus nasojejunal (NJ) feeding

►***Mortality***

One SR [159] reported on the difference in mortality in those treated with NG versus NJ nutrition.

Nasogastric feeding was associated with a non-significant reduction in the risk of death:

- NG feeding: 10/43; NJ feeding 11/36; RR 0.77; 95% CI 0.37 to 1.62; p=0.50
  Level 1+

►***Infection (includes positive blood culture, tracheal aspirate, pancreatic aspirate and bile culture)***

One study [151] reported on the infection rate in patients treated with NG versus NJ feeding. No significant difference was reported between the groups:

- NJ group: 6/14 (43%); NG group: 7/16 (44%); P=0.467; RR 0.98 (95% CI 0.43, 2.23)
  Level 1+

►***Length of stay***

Two studies [151,152] reported on length of stay in patients treated with NG versus NJ feeding. No significant difference was reported between the groups (see Table 3-18 for summary of results).

Table 3-18. Summary of results.

Length of stay				
	NG group	NJ group	Mean difference (95% CI)	P value
KUMAR 2006[151] (mean ± SD)	24.06 ± 14.35	29.93 ± 25.54	-5.87 (-20.98, 9.24)	0.437
EATOCK 2005[152] Mean (range)	16 (10-22)	15(10-42)	-	-

Level 1+

►***Operative interventions***

One study [151] reported on the number of operative interventions in patients treated with NG versus NJ feeding. No significant difference was reported between the groups.

- NJ group: 2/14; NG group: 1/16; RR 2.29 (95% CI 0.23, 22.59), p=0.48

Level 1+

Summary

►***Nutritional supplementation versus no supplementation (n=3)***

Nutritional supplementation resulted in a statistically significant reduction in:

- Mortality (Parenteral versus none and enteral versus none) [158]
- Length of stay [148,155,157]

Level 1+

Nutritional supplementation resulted in a statistically non-significant reduction in:

- Infections (Enteral versus none) [158]
- SIRS [148]
- MOF [157]
- Operative interventions [148]

Level 1+

Nutritional supplementation (parenteral versus none) resulted in a statistically non-significant increase in:

- Infections [158]

Level 1+

►***Enteral versus parenteral nutrition (n=9)***

Enteral nutrition resulted in a statistically significant reduction in:

- Infections [158]
- Length of stay [124,154,156}
- MOF [149]

Level 1+

Enteral nutrition resulted in a statistically non-significant reduction in:

- Mortality [158]
- Length of stay [146,150]
- MOF [146,147,150]

Level 1+

►***NJ versus NG (n=3)***

NG feeding resulted a non-significant reduction in:

- Mortality [158]

Level 1+

There was a statistically non-significant difference between NJ versus NG in:

- Operative interventions [151]
- Length of stay [151]
- Infections [151]

Level 1+

3.5.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No cost-effectiveness analysis was identified assessing nutritional supplementation in patients with acute alcohol-related pancreatitis. Three RCTs[124,153,161] reporting a cost-comparison assessment of the use of enteral nutrition versus parenteral nutrition were selected and presented to the GDG.

3.5.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Table 3-19presents cost-comparison assessments of the use of enteral nutrition versus parenteral nutrition in patients with acute pancreatitis. One of the three assessments presented was conducted from a United Kingdom perspective [124], and the other two were conducted from the perspective of countries with a health-care system reasonably comparable to the NHS (Canada [161] and Greece [153]). The three assessments concluded that the use of enteral nutrition is less costly than parenteral nutrition in patients with acute pancreatitis.

Table 3-20. Cost-comparison of enteral nutrition

Study (RCT)	Gupta 2003[124]	Louie 2005[161]	Kalfarentzos 1997[153]
Perspective	United Kingdom; Southampton General Hospital; between November 1996 and April 1998	Canada; between July 1999 and December 2001	Greece; between July 1990 and December 1995
Population	Patients with predicted severe acute pancreatitis (APACHE II >6)	Patients with acute pancreatitis with a Ranson's score greater than 2	Patient with acute pancreatitis
Comparators	• EN (N=8); given for a median of 2 days (2 to 7) • PN (N=9); given for a median of 4 days (2 to 7)	• EN (N=10); nasojejunal feeding tubes were placed via gastroscopy and confirmed radiographically • PN (N=18); long-term vascular catheters were placed percutaneously and confirmed	• EN (N=18); nasoenteric tube • PN (N=20); central

<table>
<tr><th>Study (RCT)</th><th>Gupta 2003[124]</th><th>Louie 2005[161]</th><th>Kalfarentzos 1997[153]</th></tr>
<tr><td></td><td></td><td>radiographically</td><td>venous catheter</td></tr>
<tr><td>Complications</td><td>No complication of feeding tube/catheter placement/replacement in both groups</td><td>The replacement or confirmation of placement of removed or dislodge nasojejunal tubes generated additional costs of $289 (£159) per EN patient</td><td>Both EN and PN were well tolerated</td></tr>
<tr><td>Direct cost</td><td>• EN cohort = £55 per patient
• PN cohort = £297 per patient</td><td>• EN = $1375 (£755)
• PN = $2608 (£1431)
• This cost includes the volume of nutrition itself and overhead costs associated with nutrition support (production of PN; placement of nasojejunal tubes or insertion of percutaneous indwelling catheters)</td><td>• EN = £30 per patient per day (mean 34.8 days)
• PN = £100 per patient per day (mean 32.8 days)</td></tr>
<tr><td>Indirect cost</td><td>Not reported</td><td><table><tr><th>Cost</th><th>EN</th><th>PN</th></tr><tr><td>Radiology
p=0.5</td><td>$735 (£403)</td><td>$852 (£468)</td></tr><tr><td>Intensive care
p=0.9</td><td>$21 022 (£11 537)</td><td>$21 495 (£11 797)</td></tr><tr><td>Operative
p=0.8</td><td>$3039 (£1668)</td><td>$4662 (£2559)</td></tr></table></td><td>Not reported</td></tr>
</table>

Abbreviations: EN = Enteral Nutrition; PN = Parenteral Nutrition

3.5.6 *FROM EVIDENCE TO RECOMMENDATIONS*

A significant reduction in mortality and length of stay was associated with provision of nutritional support either enterally or parenterally (compared to withholding feeding) and clearly supported a recommendation. Although there were no papers specifically

comparing early to late feeding, the consensus of the GDG was that feeding should be initiated soon after admission.

The GDG discussed the route for providing nutritional support. They agreed that the evidence supports enteral feeding over parenteral feeding primarily due to a reduced incidence of infection and a reduced length of stay. This evidence reflects the clinical experience of the group. Enteral feeding is also associated with reduced cost.

When discussing the type of enteral tube feeding it was apparent that the evidence did not clearly favour any particular route (NG or ND or NJ). The GDG discussed whether a recommendation could reflect this and support the most practical and non-invasive option, but it was felt that the evidence was insufficient and that there may be other benefits that were not identified in the studies conducted to date. As such, it was decided that the best approach was to make a research recommendation to determine the optimal method of delivery for people with severe acute alcohol-pancreatitis.

3.5.7 Recommendations

R32 Nutritional support for people with acute alcohol-related pancreatitis should be offered:

- early (on diagnosis)
- enterally rather than parenterally where possible.

3.5.8 Research Recommendation

RR6 What is the clinical and cost-effectiveness of nasogastric versus nasojejunal delivery of nutritional support to patients with acute severe alcohol-related pancreatitis?

3.6 Enzyme supplementation

3.6.1 Clinical introduction

Steatorrhoea and weight loss are features of chronic pancreatitis and arise because of the associated exocrine insufficiency. Steatorrhoea is caused by an increase in faecal fat due to a significant (usually over 90%) drop in pancreatic lipase production. Maldigestion of other nutrients can occur, but fat maldigestion is the first to become clinically relevant. Pancreatic enzymes are often prescribed for these manifestations of chronic pancreatitis, and once they have been started, they are often continued lifelong.

Pancreatic enzyme supplementation is also prescribed for the pain of chronic pancreatitis by some clinicians, on the basis that the exogenous enzymes may rest the pancreas and reduce endogenous enzyme production, thereby relieving the pain.

The GDG searched for evidence for the efficacy of enzyme supplementation for steatorrhoea, weight loss and pain in chronic pancreatitis. In addition, they wished to determine if there was a benefit of one formulation of enzymes over another.

Therefore the clinical question posed and upon which the literature was searched was:

> *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?*

3.6.2 Clinical methodological introduction

Studies were included that reported on the safety and efficacy of pancreatic enzymes in patients with chronic pancreatitis (predominantly alcohol-related pancreatitis) that reported on the outcomes of steatorrhoea, weight gain, abdominal pain duration of pain episodes, intensity of pain, analgesic use, absorption and wellbeing score.

Twelve studies were included in the evidence review [162-173]
Level 1+/1++

These studies were reported under the categories:
Enzyme versus placebo (N=7)
Enzyme versus enzyme (N=3)
Comparisons of different doses (N=2)

Two studies were excluded from the review because they were of low quality with no reporting on randomisation, allocation concealment or blinding [174,175].
Level 1-

Eleven of the twelve studies were cross-over trials, however only two of these studies reported on a wash-out period between treatments [162,170]. The overall quality of the studies was low, in nine studies the method of randomisation was poor or unclear [163,165-168,170-173]; in nine studies allocation concealment was unclear [162-165,167,168,170,171,173] and in ten studies the method of blinding was unclear [163,165,167-173]. Two studies also had high drop out rates, between 22-23% [167,170].

3.6.3 Clinical evidence statements

Steatorrhoea/ faecal fat

►Placebo versus pancreatic enzyme

Four studies comparing a pancreatic enzyme preparation with placebo reported on change in faecal fat [164,168,172,176]. Two studies reported a significant difference in faecal fat reduction when comparing pancreatic enzyme preparations with placebo [168,172]. One study reported a significant reduction in faecal fat with enzyme preparation compared to placebo in patients with steatorrhoea [164]. See Table 3-21below.

Level 1+

Table 3-21. Summary of results.

STUDY	Pancreatic enzyme preparation	Mean Faecal Fat: g/day (after treatment)	Mean difference (versus placebo)	% mean reduction (from basal value)	P value (compared to placebo score)
MOSSNER[169]	Panzytrat 20 000	11	-	25	NS*
HALGREEN[164]	Pancrease 25 000	Patients with steatorrhoea: 10.4	-	-	<0.01
		Patients without steatorrhoea: 3.3	-	-	NS
O'KEEFE[172]	Creon	20.3	-27.70 [-33.66, -21.74]	-	<0.0001
DELCHIER[168]	Eurobiol 25 000	24	-10.00 [-17.21, -2.79]	-	0.007
	Eurobiol	32	-18.00 [-21.80, -14.20]		<0.001

* This result may have been affected by the inclusion of 10 patients (23%) who had normal faecal fat excretion at the start of the study [176].

Level 1+

One study used a symptom score to measure steatorrhoea and reported no significant difference between the placebo and pancreatic enzyme preparation [162].

Level 1++

►***Enzyme versus enzyme/Comparisons of different doses:***

Three studies comparing different pancreatic enzyme preparations reported on change in faecal fat [165,167,170]. One study reported on change in faecal fat when looking at different dosing of pancrease [173]. See Table 3-22below

Table 3-22. Summary of results.

STUDY	Pancreatic enzyme preparation	Faecal Fat: g/day	% mean reduction	P value (compared to basal score)
DELHAYE[170]	Pancrease HL	10.68 ± 0.66	-	NS

GOUEROU[167]	Pancrease	13.9 ± 12.96	40	NS*
DELHAYE[170]	Pancrease HL + omeprazole	9.52 ± 0.71	-	0.03
VECHT[173]	Pancrease, 10,000 + omeprazole	17.9 ± 6.5	51	<0.01
	Pancrease, 20,000 + omeprazole	18.3 ± 4.7	50	<0.01
LANKISCH[165]	Kreon	12.6	79	<0.05
DELHAYE	Creon 3	10.26 ± 0.61	-	NS
	Creon 3 + omeprazole	9.14 ± 0.56	-	0.03
LANKISCH	Pankreon 700	33.5	44	NS*
	Pankreon 700 + cimetidine	23.6	60	NS*
GOUEROU[167]	Eurobiol	12.32 ± 9.48	46	NS

* These studies included patients without steatorrhoea and this may have affected the result [162,164]

NS = not significant

Level 1+

Weight gain

►***Placebo versus pancreatic enzyme***

Two studies which compared a pancreatic enzyme preparation with placebo reported on the outcome body weight. Patients randomized to receive pancreatin gained 3.6-5.5kg in body weight over the 8 week period compared to no weight gain in those randomized to placebo [171].

Level 1+

►***Enzyme versus enzyme***

One study comparing different pancreatic enzyme preparations reported on body weight. No significant change in body weight was seen between day 0 compared to day 56 at which point all the different enzyme preparations had been taken [170].

Level 1+

►***Comparisons of different doses***

One study comparing regular dosing of a pancreatic enzyme (as recommended by the manufacturer) with individually administered dosing (symptom triggered) found no significant change in weight between the two dosing regimens [166].

Level 1+

Abdominal pain (duration of pain episodes, intensity of pain and analgesic use)

►***Placebo versus pancreatic enzyme***

Six studies comparing pancreatic enzyme preparations with placebo reported on change in pain [162-164,169,171,172].

Level 1+

Three studies reported no significant change in pain scores between the placebo and pancreatic enzyme preparation [164,169,171].

Two studies reported an improvement in pain scores when using pancreatic enzyme supplementation compared with placebo [162,163]:

- Examiner rated pain was significantly lower when patients were on pancreatic enzyme compared with placebo (N=1)
- The patient-rated mean pain score during the week was significantly lower when patients were on enzyme supplementation compared with placebo (N=1)
- The examiner-rated mean pain score was significantly lower on pancreatic enzyme compared with placebo (N=1)
- The frequency of pain was significantly lower in patients on enzyme supplementation compared with placebo (N=1)
- For patients with mild to moderate disease the average daily pain score was significantly lower on enzyme supplementation compared with placebo (N=1).

Level 1+

Two studies saw a reduction in pain when comparing a pancreatic enzyme preparation to placebo [162,163] :

- 15/19 had pain relief during the week on pancreatic enzyme treatment compared with placebo (N=1)
- Patients with mild to moderate impairments of exocrine function (maximum bicarbonate concentration in the secretin test between 50 and 80 mEq/L and normal faecal fat determination) had significantly more pain relief with enzyme supplementation than placebo (N=1)
- 75% with mild to moderate disease experienced pain relief with enzyme supplementation compared to 25% of patients with severe disease (steatorrhoea) (statistically non-significant difference) (N=1)

Level 1+

Two studies reported no significant change in abdominal pain when comparing placebo with a pancreatic enzyme preparation. [164,172].

Level 1+

Two studies reported no significant change in analgesic use when comparing placebo with a pancreatic enzyme preparation [164,169]. However, one study reported a 40% reduction in the use of analgesics [163].

Level 1+

►***Enzyme versus enzyme***

Two studies comparing different enzyme preparations found no significant change in pain [167,170].

Level 1+

►***Comparisons of different doses***

One study comparing different doses of a pancreatic enzyme preparation reported a significant reduction in abdominal symptoms score with both doses compared to basal values (0-10).

Level 1+

One study reporting on different dosing regimes reported a significantly lower pain score during the self-administration of pancrease.

Level 1+

Wellbeing score

►***Placebo versus pancreatic enzyme***

One study reported on patients' general wellbeing and found no significant difference between the placebo and enzyme group, however no data were provided, so the exact difference could not be assessed [164].

Level 1+

►***Enzyme versus enzyme***

One study reported on this outcome and found no significant change in wellbeing score during the four treatment periods, however no data was provided [170].

Level 1+

►***Comparisons of different doses***

One study reported on this outcome and found a significant improvement in wellbeing score when using both doses of pancrease in comparison to basal values [173].

Level 1+

Absorption

►***Placebo versus pancreatic enzyme***

Two studies comparing a pancreatic enzyme preparation with placebo reported results on the outcome absorption [171,172]. Both studies reported a significant increase in fat absorption when taking the pancreatic enzyme preparation compared to placebo.

Level 1+

One study reported a non-significant improvement in carbohydrate and protein absorption when using a pancreatic enzyme preparation compared to placebo [171]. However they did report a significant increase in total energy absorption when using a pancreatic enzyme preparation.

Level 1+

►***Enzyme versus enzyme***

One study comparing different enzyme preparations reported on the change in fat and protein absorption. No significant difference in fat or protein absorption was found between different enzymes or with or without the addition of omeprazole [170].

Level 1+

►***Comparisons of different doses***

One study reported difference in fat absorption when using different doses of a pancreatic enzyme preparation. They found a significant increase in fat absorption in both treatment groups (pancrease 10,000 and pancrease 20,000) compared to placebo.

Level 1+

Subgroup: Studies looking at pancreatic enzymes in combination with H_2 blockers versus pancreatic enzymes alone.

►***Steatorrhoea/ faecal fat***

One study [170] reporting fat excretion (g/day) saw no significant difference with the addition of omeprazole to pancrease or creon.

Level 1+

One study [165] reported a significant reduction in faecal fat with the addition of cimetidine or when using the pH sensitive enzyme preparation Kreon compared to a non-significant reduction with pankreon alone.

Level 1+

►*Weight gain*

No results were reported on the difference with and without the addition of an H2 blocker.

►***Abdominal pain (duration of pain episodes, intensity of pain and analgesic use)***

One study [170] reported no significant difference in the severity of abdominal pain with Creon or Pancrease HL with or without the addition of omeprazole.

Level 1+

►*Wellbeing score*

One study [170] reported no significant difference in general wellbeing with Creon or Pancrease HL with or without the addition of omeprazole.

Level 1+

►*Absorption*

One [170] reported no significant difference in percentage fat or protein absorption with Creon or Pancrease HL with or without the addition of omeprazole.

Level 1+

Limitations of evidence:

The small sample size of most of these studies (range N=6-43) may have left the studies underpowered to detect a significant change in any of the reported outcomes. All of the studies were reporting on short-term use of pancreatic enzymes (24 hours to 30 days per treatment), which may not have allowed time for the enzymes to take full effect.

3.6.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No relevant economic analysis was identified assessing the cost-effectiveness of pancreatic enzyme supplementation in patients with alcohol-related pancreatitis. The cost of drugs used for pancreatic enzyme supplementation was presented to the GDG[43].

3.6.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

In NHS current medical practice, pancreatic enzyme supplementation is given to a large number of patients suffering from chronic alcohol-related pancreatitis, primarily as a means for controlling pain. Creon® is the drug most frequently used and doses required for managing patients with chronic alcohol-related pancreatitis are generally higher than doses recommended in the BNF No. 56 (6-8 capsules with meals instead of 1-2 capsules). Generally, using Creon® for pancreatic enzyme supplementation is more costly than using other drug options[43].

3.6.6 *FROM EVIDENCE TO RECOMMENDATIONS*

The small sample size of most of these studies (range N=6–43) means that they may be underpowered to detect a significant change in any of the reported outcomes. All of the studies were reporting on short-term use of pancreatic enzymes (24 hours to 30 days per treatment), this may not have allowed time for the enzymes to produce a clinically significant effect.

A number of studies included dietary intervention (moderation of fat intake) and moderation of alcohol intake.

The studies in general showed a reduction in faecal fat in those patients on pancreatic enzyme supplementation. The GDG felt that this was important in terms of symptom control (steatorrhoea) and with regard to calorie and fat soluble vitamin absorption in the longer term. In spite of the short length of the studies, there was also some evidence for weight gain with enzyme supplementation to support their use.

The GDG felt that there was not sufficient evidence to support the use of enzyme supplements for pain related to chronic pancreatitis. While there may be patients with pain that require enzyme supplementation for other reasons, supplementation should not be used as a treatment for pain or in those patients with pain without steatorrhoea or weight loss. These patients should be managed with reference to the specific guidance on the management of pain associated with chronic pancreatitis (seeChapter 3.3).

As there is no clinical evidence favouring one enzymatic preparation over another, the GDG felt that the choice of which one to prescribed should be based on cost. It was noted that acid suppression may be required in addition to enzyme supplementation when the 'older' formulations are used which are not microencapsulated. This would involve additional costs.

In summary, it was felt that there was sufficient evidence to recommend enzyme supplementation to improve nutritional status and steatorrhoea in patients with pancreatic exocrine insufficiency, but not for pain alone.

3.6.7 *RECOMMENDATIONS:*

R33 Offer pancreatic enzyme supplements to improve steatorrhoea and nutritional status in people with exocrine pancreatic insufficiency secondary to alcohol-related chronic pancreatitis.

R34 Do not prescribe pancreatic enzyme supplements if pain is the only symptom of chronic alcohol-related pancreatitis.

APPENDICES

A.1. CORTICOSTEROIDS VERSUS PLACEBO FOREST PLOTS

Corticosteroids vs placebo (patients with DF ≥ 32 or encephalopathy)

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.1 Mortality - all cause (one month).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.2 Mortality - all cause (6 months).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.3 Mortality - liver related (28 days).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.4 Mortality - liver related (6 months).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.5 Gastro-intestinal bleeding.

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.6 Infection.

Corticosteroids versus placebo (patients with DF ≥32)

Forest plot of comparison: 1 Corticosteroids vs placebo (all patients), outcome: 1.1 Mortality - all cause (one month).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.2 Mortality - all cause (6 months).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.3 Mortality - liver related (28 days).

Forest plot of comparison: 1 Corticosteroids vs placebo (severe hepatitis patients), outcome: 1.4 Mortality - liver related (6 months).

A.2. CLINICAL QUESTIONS AND LITERATURE SEARCHES

Question ID	Question wording	Study Type Filters used	Databases and Years
BENZO	*'What is the safety and efficacy of a benzodiazepine (chlordiazepoxide or diazepam, alprazolam, oxazepam, clobazam, lorazepam) versus a) placebo b) other benzodiazepines benzodiazepine (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?'*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
NEUROLEP	*"What is the safety and efficacy of a) neuroleptic agents, promazine hydrochloride, haloperidol, clozapine, risperidone, olanzapine, quetiapine) versus placebo b) other neuroleptic agents c) neuroleptic agents in combination with benzodiazepines (diazepam, chlordiazepoxide, alprazolam, oxazepam, clobazam, lorazepam) for patients with DTs?"*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

Question ID	Question wording	Study Type Filters used	Databases and Years
DIAZ	*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?*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
DIAG1	*'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?* *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?'*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
DETOX	*'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?'*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

Question ID	Question wording	Study Type Filters used	Databases and Years
TRANSP	*What length of abstinence is needed to establish non-recovery of liver damage, which thereby necessitates referral for consideration for assessment for liver transplant?*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
NURS	*1) What is the accuracy of a tool and/or clinical judgement for the a) assessment b) monitoring of patients at risk of acute alcohol withdrawal?* *2) Does the assessment and monitoring of patients with acute alcohol withdrawal improve patient outcomes?*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
DIAG2	*'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?'* *'What is the safety and accuracy of laboratory and clinical markers versus liver biopsy for the diagnosis of alcohol related hepatitis versus decompensated cirrhosis?'*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

Question ID	Question wording	Study Type Filters used	Databases and Years
SURG	*1) 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?* *2) 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?* *3) 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?* *4) 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?*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
ENZYME	*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?*	None	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

Question ID	Question wording	Study Type Filters used	Databases and Years
NUTRI4	a)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* *b) Which patients are at risk of developing Wernicke's encephalopathy and therefore require prophylactic treatment?*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
ANTIBIO	*In patients with acute alcohol-related pancreatitis, what is the safety and efficacy of prophylactic antibiotics versus placebo?*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
NUTRI2	*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 hrs) vs late supplementation c) NJ vs NG) vs parenteral nutrition?*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

Question ID	Question wording	Study Type Filters used	Databases and Years
DIAG3	*"What is the diagnostic accuracy of abdominal ultrasound versus computed tomography (CT) for the diagnosis of alcohol-related chronic pancreatitis?"*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
NUTRI1	*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*	**Systematic Reviews, RCTs, Comparative and Observational Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009
CORTICO	*'In patients with acute alcohol-related hepatitis, what is the safety and efficacy of corticosteroids versus placebo?'*	**Systematic Reviews, RCTs, Comparative, Observational and Diagnostic Studies**	Medline 1950-2009 Embase 1980-2009 Cinahl 1982-2009 Cochrane 1800-2009

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2

A.3. HEALTH ECONOMIC ANALYSIS – DOSING REGIMENS FOR ACUTE ALCOHOL WITHDRAWAL

1. Background

Acute alcohol withdrawal (AAW) is a medical condition that manifests in alcohol-dependent patients who reduce or discontinue their alcohol intake. The symptoms associated with this condition range over a spectrum of severity from mild to moderate (tremor, restlessness, insomnia, nausea and tachycardia) to the more severe (seizures and delirium tremens). The clinical evidence review showed that benzodiazepines were more effective than placebo for the prevention of delirium tremens and alcohol withdrawal seizures[26]. In addition, benzodiazepines were not found to be more efficient than neuroleptics, carbamezepine, and clomethiazole for the treatment of patients with AAW[26].

Different management options are available for the assessment and monitoring of patients with AAW. The symptom-triggered dosing regimen of benzodiazepines was associated with significantly lower doses of benzodiazepines[32] and shorter treatment duration compared to a fixed-dosing regimen[30,31,33]. A quality of life assessment found that a symptom-triggered dosing regimen improved patients' physical functioning compared to the fixed-dosing regimen ($p<0.01$)[30]. The fixed-dosing regimen is the most commonly used method in general hospitals across England and Wales.

The Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-A) and its revised form, the CIWA-Ar, are validated scales applied for managing patients with AAW. The CIWA-Ar was the scale used in the clinical studies comparing symptom-triggered and fixed-dosing regimens included in this review[30-33]. The CIWA-Ar scale was reported to be valuable for identifying patients in the general hospital setting who are in early withdrawal and require drug therapy to avoid complications[50]. The CIWA-Ar scale and a recently revised version, the CIWA-AD, are used in England and Wales where the symptom-triggered regimen forms part of the AAW management protocol.

There are different cost implications associated with each type of dosing regimen. In addition to the difference in drug cost, the duration of treatment could have a large impact on the hospital length of stay and related costs. Similarly, each dosing regimen has different training and implementation implications and demands different amount of staff resource (to assess and monitor patients).

The length of hospital stay is impacted directly by the regimen used when a patient is admitted for the treatment of the AAW syndrome alone[30,31,33]). However, when a patient is admitted for a co-morbid condition, the regimen is not the key determinant of the patient's length of stay[32]).

There is a lack of health economic evidence on this topic. From a systematic literature search, no relevant cost-effectiveness evidence was identified that compared treatment regimens for use in people with AAW. This cost-effectiveness analysis was therefore undertaken to discern whether the symptom-triggered regimen is a cost-effective option to use for the NHS in England and Wales.

2. Objective

The objective of this economic analysis was to assess the cost-effectiveness of the fixed-schedule dosing regimen of benzodiazepines or clomethiazole, compared to a symptom-triggered dosing regimen, for the in-hospital management of patients with acute alcohol withdrawal in England and Wales.

This economic analysis had mainly considered the experience of implementing and using the symptom-triggered regimen in the Addenbrooke's Hospital (Cambridge), the Huntercombe Centre (Sunderland), and the Royal Liverpool and Broadgreen University Hospital Trust.

3. Model

Four cost-effectiveness analyses were conducted, each based on a different clinical study comparing the symptom-triggered regimen with the fixed-dosing regimen. Two populations of patients were considered: patients with AAW admitted for the treatment of this condition alone; and patients with AAW admitted for a co-morbid medical condition. The health outcome considered for this analysis was the Quality-Adjusted Life Year (QALY). This analysis was conducted from an England and Wales NHS perspective, with a time horizon extending to the end of the hospital admission.

4. Clinical studies

Four studies [30-33] met the inclusion criteria for the clinical literature review as outlined in the methods chapter at the beginning of the guideline. Three were conducted using patients admitted for AAW only (Daeppen 2002[30], Saitz 1994[31], Lange-Asschenfeldt 2003[33]) whilst one study (Weaver 2006[32]) considered a population of patients with AAW admitted for a co-morbid condition. Table 1 summarises the results of these studies.

Table 1

Clinical studies						
Study	**Type of study**	**Drug used**	**Symptom-triggered**		**Fixed-schedule**	
			Mean duration of treatment (hours)	**Mean dose of drug (mg)**	**Mean duration of treatment (hours)**	**Mean dose of drug (mg)**
Daeppen	RCT	Oxazepam	20	37.5	63	231.4
Saitz	RCT	Chlordiazepoxide	9	100	68	425
Lange-Asschenfeldt	Retrospective analysis	Clomethiazole	101	4352	180	9921
Weaver	Quasi-randomised Trial	Lorazepam	Not reported	28.8	Not reported	102.1

These studies reported rates of complications for developing delirium tremens, seizures, lethargy and hallucinations, and showed no significant difference between the fixed-dosing and the symptom-triggered cohorts[30-33]. In addition, there was no significant difference between cohorts in the use of co medications[33].

A meta-analysis of results presented in Table 1 was not possible as the data are very heterogeneous. Therefore, each of the four studies was modelled in a separate cost-effectiveness analysis.

The economic modelling of the three clinical studies on patients admitted for AAW only (Daeppen 2002[30], Saitz 1994[31], and Lange-Asschenfeldt 2003[33]) considered the difference in length of hospital stay between the two cohorts. In the Weaver study[32] (where patients were admitted for a co-morbid condition) there was no difference in the length of hospital stay between the trial arms as the co-morbid condition determined the length of hospital stay.

5. QALYs

Utility scores were obtained for each regimen by applying the SF-6D algorithm[42] to the original SF-36 data from the Daeppen study[30]. The difference in utility scores between the cohorts was marginal (0.0194) and non-significant (95% CI, -0.00972 to 0.4843; p=0.19) (Table 2).

The Daeppen study[30] assessed health-related quality of life (SF-36) at 3 days post start of treatment and asked the patients to judge their health-related quality of life (HRQoL) over the past 3 days for both the symptom-triggered and the fixed-dosing cohorts. QALYs were calculated by multiplying the utility score by the 3 days' duration for each arm. In the base case analysis, it was assumed that there would be no HRQoL difference between the cohorts after 3 days, and the Daeppen QALY gain was applied to the other studies (Table 2).

Table 2

Health outcomes						
	Population (Deappen)	Utility scores		Duration	Quality adjusted life-years (QALYs)	
Regimen	**N**	**Mean**	**Std. deviation**	**Days (Deappen)**	**QALYs**	**QALY difference**
Symptom-triggered	56	.6614	.07376	3	.005436	.000159
Fixed-dosing	60*	.6420	.08423	3	.005277	

* Data from one patient were excluded as they were reported incorrectly.

6. Cost

Four categories of cost were considered in this analysis: treatment; hospitalisation; staff time for a nurse monitoring a patient with AAW; and the cost of implementing the symptom-triggered regimen.

6.1. Treatment cost

In the base-case analysis, for each of the four cost-effectiveness models, the UK cost of the oral drugs used in the respective studies was included (Table 1). Table 3 shows the price of the drugs used in this study.

Table 3

Drug price	
Drug	**Price**
Chlordiazepoxide Hydrochloride	5mg tablet; 20-tab pack = £0.50
Lorazepam	1mg tablet; 28-tab pack = £8.28
Oxazepam	10mg tablet; 28-tab pack = £6.17
Clomethiazole	192mg capsule; 60-caps pack = £4.78

Source: BNF No. 57, March 2009[117].

This drug cost was varied in a one-way sensitivity analysis by substituting the price of other drug options to see if it affected the results of the analysis (Table 4).

Table 4

Drug cost – sensitivity analysis*		
Study	**Drug used in the study**	**Drug(s) for the sensitivity analysis****
Daeppen	Oxazepam	Chlordiazepoxide
Saitz	Chlordiazepoxide	Oxazepam
Lange-Asschenfeldt	Clomethiazole	Not applicable***
Weaver	Lorazepam	Chlordiazepoxide / Oxazepam

* The sensitivity analysis considered the cost of using chlordiazepoxide and oxazepam (two widely used drugs for in-hospital treatment of patients with AAW in England and Wales).
** The equivalent drug doses used were: Chlordiazepoxide 15mg; Oxazepam 15mg; Lorazepam 0.5mg[177]
*** It is not possible to convert the dose of clomethiazole to that of a benzodiazepine.

6.2. Hospitalisation cost

Hospitalisation cost was estimated by multiplying the duration of treatment reported in the clinical studies (Table 1) by the average cost of an inpatient day.

A patient with AAW can be admitted to a number of different services/specialty settings and Table 5 summarizes these costs per in-patient day. The average cost for treating patients with AAW across all trusts in England and Wales was estimated to be £219 per in-patient day[178]. This cost was used in the base-case analysis for the three modelled clinical studies where there was a difference in length of stay between the cohorts(Daeppen 2002[30], Saitz 1994[31], Lange-Asschenfeldt 2003[33]. A one-way sensitivity analysis considered other inpatient costs: £254 and £271 per inpatient day[178] (Table 5).

Table 5

Inpatient cost	
NHS Service	**Cost per inpatient day**
NHS inpatient treatment for people who misuse drugs/alcohol	£219 *
A&E Observation ward	£271 **
All specialities (Weighted average)	£254 **
Acute NHS hospital services for people with mental health problems	£219 *

* Source: Unit Costs of Health and Social Care 2008[178].
** Source: National Schedule of Reference Costs 2006-07 - NHS Trusts[97].

6.3. Staff time cost

The cost of staff time was calculated by multiplying the hourly cost of nurse time (Table 8) by the time a nurse is in contact with a patient. The amount of time a nurse is in contact with the patient is determined by the assessment schedule used by the nurse monitoring the patient and the number of minutes required to conduct each assessment.

6.3.1. Assessment schedule

Clinical studies did not report the time a nurse was in contact with a patient during the monitoring process, but reported the protocols used for each regimen. Table 6 summarises the assessment schedules used in the clinical studies for both symptom-

triggered and fixed-dosing regimens. It also presents schedules from a selection of hospitals, as submitted by GDG members.

Table 6

Clinical study protocols for symptom-triggered regimens			
Daeppen 2002*	**Saitz 1994***	**Weaver 2006***	**Lange-Asschenfeldt 2003***
▪ > 8: every 30 minutes ▪ < 8: every 6 hours	▪ > 8: hourly ▪ < 8: every 6 hours	▪ > 30: hourly ▪ < 30: every 4 hours	▪ Every 2 hours (day 0-3) ▪ Every 4 hours (day 4-5; mean duration of treatment: 4.2 days)
UK protocols for symptom-triggered regimens			
Royal Liverpool and Broadgreen University Hospital Trust**	**Addenbrookes Hospital***	**Huntercombe Centre, Sunderland****	**Greenwich PCT (based on St Thomas' Hospital)***
▪ Hourly (independent of score) ▪ Every 4 hours (when symptom controlled)	▪ 0-5: every 4 hours ▪ 6-8: every 2 hours ▪ > 9: hourly	▪ < 20: every 4 hours ▪ > 20: hourly	▪ Every 2 hours (only for first 24 hours; followed by a fixed-dosing regimen)
Clinical study protocols for fixed-dosing regimens			
Daeppen 2002	**Saitz 1994**	**Weaver 2006**	**Lange-Asschenfeldt 2003**
▪ 4 times a day ▪ As-needed medication	▪ 4 times a day ▪ As-needed medication	▪ 6 times a day ▪ As-needed medication	▪ Day 0-2: 3/4 times ▪ Day 3-4: 2/3 times ▪ Day 5-9: tapered
UK protocols for fixed-dosing regimens			
Royal Liverpool Hospital Trust	**Derby Hospital**	**Imperial College Healthcare Hospital**	**University Hospital Bristol**
▪ Day 1-3: 4 times ▪ Day 4-6: 3 times ▪ Day 7: 2 times ▪ Day 8-9: 1 time ▪ No PRN	▪ Day 1-5: 4 times Day 6: 3 times ▪ Day 7: 1 time ▪ No PRN	▪ Day 1-6: 4 times ▪ Day 7: 3 times ▪ Day 8: 2 times ▪ Day 9: 1 time ▪ No PRN ▪ Severe AAW: 1 PRN 1st day	▪ Day 1-5: 4 times ▪ Day 6: 2 times ▪ Day 7: 1 time ▪ 2 PRN (day 1 & 2)
Cambridge University Hospitals	**Greenwich PCT (based on St Thomas' Hosp)**	**Maudsley prescribing guideline**	**Royal Free Hampstead NHS Trust**
▪ Day 1: 3/4 times + PRN ▪ Day 2: 3 times + PRN ▪ Day 3: 3 times + PRN ▪ Day 4: 2 times + PRN ▪ Day 5: 3 times + PRN ▪ Day 6: 2 times + PRN ▪ Day 7: 1 time, no PRN	▪ Begin after 24 hrs of symptom-triggered ▪ 4 times a day ▪ No PRN	▪ Day 1-4: 4 times ▪ Day 5: 2 times ▪ No PRN	▪ Chlordiazepoxide o Day 1-4: 4 times + prn o Day 5: 2 times + prn o Day 6: 1 time + prn ▪ Clomethiazole o Day 1-3: 3/4 times + prn (1-2) o Day 4-5: 2/3 times + prn (1-2) o Day 6-7: Tapered

* Protocol using the CIWA-Ar scale

** Protocol using the CIWA-AD scale

On the basis of the protocols described in Table 6 and the clinical experience of the GDG, the fixed-dosing regimen the base-case analyses assumed was one assessment every four hours for the first 48 hours (4 doses + 2 PRN), then one every six hours. For the symptom-triggered regimen, the base-case analyses assumed one hourly assessment for the first 12 hours and one every four hours thereafter.

A sensitivity analysis considered extreme scenarios of assessment scheduling favouring either the symptom-triggered regimen or the fixed-dosing regimen (Table 7).

Table 7

Assessment schedules		
	Symptom-triggered Assessment schedule	**Fixed-schedule Assessment schedule**
Base case analysis		
	Hourly for 12 hours, then every 4 hours	Every 4 hours for 48 hours, then every 6 hours
Sensitivity analysis		
Scenario favouring symptom-triggered regimen	Hourly for 6 hours, then every 4 hours	Every 4 hours
Scenario favouring fixed-dosing regimen	Hourly for 24 hours, then every 4 hours	Every 6 hours

6.3.2. Treatment duration

The treatment durations for the three studies[30,31,33] on populations of patients admitted for treating AAW only are reported in Table 1.

The Weaver study[32] (population of patients treated for AAW admitted for a co-morbid condition) did not report treatment duration but detailed a four-day protocol[f] for the fixed-dosing regimen. The average of the ratios of treatment duration with symptom-triggered and fixed-dosing regimens from the 3 studies reporting it is 33.7%[30,31,33]. Using this ratio and considering that the treatment duration for the fixed-dosing regimen is 96 hours in the Weaver study, the treatment duration for the symptom-triggered regimen was estimated to be 32 hours for this study.

Using the assessment schedules determined by the GDG and the treatment durations from the four respective studies, we calculated the number of assessments per patient (Table 8).

Table 8

Number of assessments used in the base case analyses				
Study	**Symptom-triggered**		**Fixed-schedule**	
	Duration of treatment (hours)	**Number of assessment**	**Duration of treatment (hours)**	**Number of assessment**
Daeppen	20	14 *	63	15 **
Saitz	9	9 *	68	15 **
Lange-Asschenfeldt	101	34 *	180	34 **
Weaver	32	17 *	96	20 **

* Hourly assessment for the first 12 hours, then one every four hours.

** Every four hours for the first 48 hours, then one every six hours.

Using the alternative assessment schedules from Table 7, we re-estimated the number of assessments for a scenario sensitivity analysis – refer to Table 9.

Table 9

Number of assessments used in the sensitivity analyses

[f] First 48 hrs: Lorazepam 2 mg every 4 hrs (total 12 doses) / Tapering: 1 mg every 4 hrs for 6 doses (24 hrs), followed by 0.5 mg every 4 hrs for 6 doses (24 hrs), then discontinued.

Study	Symptom-triggered regimen	Fixed-dosing regimen	Scenario in favour of symptom-triggered regimen - Number of assessment		Scenario in favour of fixed-dosing regimen - Number of assessment	
	Duration of treatment (hours)	Duration of treatment (hours)	Symptom-triggered	Fixed-dosing	Symptom-triggered	Fixed-dosing
Daeppen	20	63	10	16	20	11
Saitz	9	68	7	17	9	11
Lange-Asschenfeldt	101	180	30	45	43	30
Weaver	32	96	13	24	26	16

6.3.3. Nurse time

To reflect clinical practice, for costing nurses monitoring patients with AAW we used a band 5 nurse. A one-way sensitivity analysis considered a band 6 nurse (Table 10).

Table 10

Nurse time cost	
Nurse band	**Cost per hour***
Band 5	£23
Band 6	£29
Band 7	£33

* Source: Unit Costs of Health and Social Care 2008[178].

The GDG estimated the average time a nurse is in contact with a patient for one assessment to be 5 minutes in both dosing regimens. This time was varied in a scenario sensitivity analysis using 7 minutes for the symptom-triggered regimen and 3 minutes for the fixed-dosing regimen.

6.4. Implementation costs

The cost of implementing the symptom-triggered regimen in services currently using fixed-dosing regimen was considered in this analysis. This includes the cost of training nurses who will manage patients with AAW, and supervision costs (post-training) for these nurses.

This analysis was based on the experience of implementing and using the symptom-triggered regimen primarily in the Addenbrooke's Hospital (Cambridge), the Huntercombe Centre (Sunderland), and the Royal Liverpool and Broadgreen University Hospital Trust.

6.4.1. Training

The estimated cost of training nurses to use the symptom-triggered regimen assumes that this training is done in-house. The training takes one hour and is delivered by an alcohol nurse specialist (band 7) to the nurse monitoring patients with AAW (band 5). It was conservatively assumed that this training is effective for one year. The hourly cost of nurse time is £23 for band 5 nurses and £33 for band 7 nurses[178] (Table 10).

- Cost of training per nurse: (1 hour per training * (£23 per hour + £33 per hour)) * 1 year efficiency of training = £56

The cost for one nurse monitoring one patient assumes that the nurse works 207 days per year[g, 178]. Whilst the number of patients a nurse manages using the symptom-triggered regimen varies in different environments[h], the conservative number of two patients per day was used in this analysis.

- Cost of training per nurse per patient: £56 / 207 working days / 2 patients monitored per day = £0.14

6.4.2. Supervision post-training

From the experience of implementing the symptom-triggered regimen in the Addenbrooke's Hospital (Cambridge), the alcohol nurse specialist (band 7) spent one week (5 days) supporting the staff post training during one hour per day, and currently oversees them for approximately 20 minutes per day. To calculate the supervision time, we considered the previous assumption that a nurse works 207 days per year[178] (7.5 hours a day), and that the training is effective for one year.

- Supervision time: ((5 days * 1 hour) + ((1/3 hour / 7.5 hours a day) * (207 working days – 5 days)) * 1 year efficiency of training = 14 hours

The total supervision cost was calculated considering that the hourly cost of nurse time is £33[178] for band 7 nurses (Table 10).

- Supervision cost: 14 hours * £33 = £461

To calculate this cost per nurse monitoring patients with AAW, we assumed that ten nurses are needed every time to manage all patients treated for AAW (using data from the Royal Free Hospital [Table 11], and using the previous assumption that one nurse monitors two patients per day [7,697 patients / 365 days / 2 patients = 10].

- Supervision cost per nurse: £461 / 10 nurses = £46.1

The supervision cost per nurse per patient was calculated by assuming one nurse monitors two patients per day (previous assumption), and that a nurse works 207 days per year[178].

- Supervision cost per nurse per patient: £46.1 / 2 / 207 = £0.11

Table 11

Royal Free Hospital – Alcohol-related finished consultant episodes (1 April 2005-31 March 2006)			
Assessment variable	**AAW 1st diagnosis**	**AAW Non-1st diagnosis**	**Total**
Finished consultation episodes (n)	221	727	948
Average stay (days)	4.4	9.2	8.1
Bed-days (n)	975	6,722	7,697

Source: Data from the Royal Free Hospital, London

[g] 29 days annual leave; 8 statutory leave days; 5 study/training days; 12 sicknesses leave; 5-day working week.

[h] The number of patients a nurse monitors using the symptom-triggered regimen is: 3 per day (Huntercombe Centre); 8-10 per week (Addenbrookes Hospital); 10 patients per day (Royal Liverpool and Broadgreen University Hospital Trust).

7. Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were performed to assess the robustness of the results to plausible variations in the model parameters.

7.1 Deterministic sensitivity analysis

The deterministic sensitivity analysis was conducted using two approaches: one-way sensitivity analysis; and scenario sensitivity analysis.

The one-way sensitivity analysis involved varying the treatment cost (Section 6.1), the hospitalisation cost (Section 6.2), and the staff time cost (using the hourly time cost of a band 6 nurse instead of a band 5 nurse – Section 6.3.3). In addition, for the three analyses done on populations of patients admitted for AAW only[30,31,33], the hospitalisation cost was removed. The scenario sensitivity analysis varied the staff time cost (using alternative scenarios of assessment schedule – Section 6.3.1 & 6.3.2; and also varying the time a nurse is in contact with a patient for one assessment – Section 6.3.3).

7.2 Probabilistic sensitivity analysis

For the probabilistic sensitivity analysis, probability distributions were assigned to specific model parameters (dose of drug; treatment duration; hourly cost of nurse time; utility score – Table 12). The main results were re-calculated 5000 times, with all of the model parameters set simultaneously, selected at random from the respective parameter distribution. We used a Beta distribution to vary the utility scores because this distribution is bounded between 0 and 1, which are the extreme values of the utility score; for the three other parameters, we used a Gamma distribution (bounded at 0), because these parameters affect cost estimates[179].

The parameters not directly varied in the probabilistic sensitivity analysis were all varied indirectly by the chosen parameters: (1) the drug costs were varied by the dose of drug; (2) the hospitalisation cost was varied by the treatment duration; (3) the staff time costs were varied by the treatment duration and by the hourly cost of nurse time; (4) the implementation cost was varied by the hourly cost of nurse time; and (5) the QALY estimates were varied by the utility score.

Table 12

Parameters used in the probabilistic sensitivity analysis				
Description of variable	**Mean value**	**Probability distribution**	**Parameters**	**Source**
SYMPTOM-TRIGGERED REGIMEN				
Dose of drug (mg)				
Daeppen (N=56)	37.5 SD = 81.7	Gamma	α = 0.211 β = 177.997	Mean and SD from Daeppen
Saitz (N=51)	100 SD = 81.7	Gamma	α = 1.498 β = 66.749	Mean from Saitz and SD from Daeppen
Lange-Asschenfeldt (N=33)	4352 SD = 4589	Gamma	α = 0.899 β = 4838.906	Mean and SD from Lange-Asschenfeldt
Weaver (N=91)	28.8 SD = 81.7	Gamma	α = 0.124 β = 231.687	Mean from Weaver and SD from Daeppen
Treatment duration (hour)				

Daeppen (N=56)	20 SD = 24.45	Gamma	α = 0.669 β = 29.890	Mean and SD from Daeppen
Saitz (N=51)	9 SD = 24.45	Gamma	α = 0.135 β = 66.423	Mean from Saitz and SD from Daeppen
Lange-Asschenfeldt (N=33)	100.8 SD = 69.6	Gamma	α = 2.098 β = 48.057	Mean and SD from Lange-Asschenfeldt
Weaver (N=91)	32 SD = 24.45	Gamma	α = 1.713 β = 18.681	Mean from assumption (Section 6.3.2) and SD from Daeppen
Utility score (N=56)	0.6614 SD = 0.07376	Beta	α = 37.038 β = 18.962	Daeppen (Section 5)
Hourly cost of nurse time	23 SE = 2.934	Gamma	α = 61.46 β = 0.37 by assuming the 95% CI is equal to the mean ±25%	Unit Costs of Health and Social Care 2008
FIXED-DOSING REGIMEN				
Dose of drug (mg)				
Daeppen (N=61)	231.4 SD = 29.43	Gamma	α = 61.822 β = 3.743	Mean and SD from Daeppen
Saitz (N=50)	425 SD = 29.43	Gamma	α = 208.543 β = 2.038	Mean from Saitz and SD from Daeppen
Lange-Asschenfeldt (N=32)	9921 SD = 6599	Gamma	α = 2.260 β = 4389.356	Mean and SD from Lange-Asschenfeldt
Weaver (N=92)	102.11 SD = 29.43	Gamma	α = 12.038 β = 8.482	Mean from Weaver and SD from Daeppen
Treatment duration (hour)				
Daeppen (N=61)	62.7 SD = 5.44	Gamma	α = 132.843 β = 0.472	Mean and SD from Daeppen
Saitz (N=50)	68 SD = 5.44	Gamma	α = 156.25 β = 0.435	Mean from Saitz and SD from Daeppen
Lange-Asschenfeldt (N=32)	180 SD = 79.2	Gamma	α = 5.165 β = 34.848	Mean and SD from Lange-Asschenfeldt
Weaver (N=92)	96 SD = 5.44	Gamma	α = 311.419 β = 0.308	Mean from assumption (Section 6.3.2) and SD from Daeppen
Utility score (N=60)	0.642 SD = 0.07376	Beta	α = 38.52 β = 21.48	Daeppen (Section 5)
Hourly cost of nurse time	23 SE = 2.934	Gamma	α = 61.46 β = 0.37 by assuming the 95% CI is equal to the mean ±25%	Unit Costs of Health and Social Care 2008

8. Results

8.1 Deterministic results

A deterministic analysis is where cost and effect variables are analysed as point estimates[180]. Deterministic results of the base-case analysis of the four cost-effectiveness analyses found the symptom-triggered regimen dominates the fixed-dosing regimen (it was more effective and less costly – Table 13). The deterministic sensitivity analysis

showed the conclusions of the base-case analyses are robust as the symptom-triggered option always remains dominant (cost-saving) or cost-effective (Table 13).

The results were most sensitive to the assumptions about time spent per assessment. In the Weaver analysis (patients with AAW admitted for treating a co-morbid condition), if nurses spend more time on the symptom-triggered assessments than on the fixed-dosing assessments, then the symptom-triggered dosing regimen is likely to be no longer cost-saving. If the difference is more than 4 minutes per assessment then symptom-triggered is no longer cost-effective (it costs more than £20,000 per QALY gained).

Table 13

Deterministic results				
	Patients admitted for treating AAW			Patients admitted for treating a co-morbid condition
Analysis	**Daeppen**	**Saitz**	**Lange-Asschenfeld**	**Weaver**
Base case analysis				
	Dominant (£398)*	Dominant (£551)*	Dominant (£723)*	Dominant (£27)*
Sensitivity analysis				
Remove hospitalisation cost	Dominant (£6)*	Dominant (£13)*	Dominant (£2)*	n/a
Using other drug 1	Dominant (£395)*	Dominant (£557)*	n/a	Dominant (£54)*
Using other drug 2	n/a	n/a	n/a	Dominant (£16)*
Inpatient cost £254 per day	Dominant (£461)*	Dominant (£637)*	Dominant (£838)*	n/a
Inpatient cost £271 per day	Dominant (£491)*	Dominant (£679)*	Dominant (£894)*	n/a
No. of assessment (favour S-T)	Dominant (£408)*	Dominant (£559)*	Dominant (£752)*	Dominant (£43)*
No. of assessment (favour F-D)	Dominant (£379)*	Dominant (£544)*	Dominant (£698)*	Dominant (£2)*
Nurse cost - Band 6	Dominant (£399)*	Dominant (£554)*	Dominant (£723)*	Dominant (£29)*
Time per nurse assessment	Dominant (£398)*	Dominant (£551)*	Dominant (£723)*	ICER = £7,489/QALY**
Probabilistic results				
Base-case analysis	Dominant (£396)*	Dominant (£563)*	Dominant (£735)*	Dominant (£29)*

* The symptom-triggered regimen is more efficient and less costly compared to the fixed-dosing regimen (total cost saved per patient using the symptom-triggered regimen is presented).
** The symptom-triggered regimen is more effective and more costly compared to the fixed-dosing regimen; the Incremental Cost-Effectiveness Ratio (ICER) is presented (which is below the NICE threshold of £20k/QALY gained).

8.2 Probabilistic results

A probabilistic analysis applies probability distributions for key parameters and presents the empirical distribution of the cost-effectiveness results[180]. The probabilistic results of this economic analysis are in agreement with the deterministic results, showing that using a symptom-triggered regimen is cost-saving for treating patients admitted for AAW and those admitted for a co-morbid condition compared to a fixed-

dosing regimen (Table 13). However, the probability of cost-effectiveness is quite low, reflecting the lack of significance in the difference in quality of life scores in the Daeppen trial (p=0.19) (Table 14).

Table 14

Probabilistic results		
Analysis	**Incremental Net Monetary Benefit – £20,000/QALY (using symptom-triggered regimen compared with fixed-dosing)**	**Probability of symptom-triggered being cost-effective at £20k/QALY**
Daeppen	£1,683	63%
Saitz	£1,581	62%
Lange-Asschenfeldt	£1,879	63%
Weaver	£1,128	59%

9. Discussion

According to the results presented, the implementation and use of a symptom-triggered dosing regimen in patients with AAW in hospitals in England and Wales is cost-effective for the NHS, in both assessed populations of patients (those patients admitted for AAW treatment and those admitted for a co-morbid condition). Results of the four economic analyses are in agreement, even considering the large heterogeneity of trial results (drug dose and duration of treatment).

Results of the analyses conducted on the population of patients admitted for AAW treatment are mainly driven by the hospitalisation cost saved from the reduced length of hospitalisation using the symptom-triggered regimen. Results of the analyses conducted on the population of patients admitted for a co-morbid condition are mainly driven by the staff time cost saved using the symptom-triggered regimen. The sensitivity analysis illustrated the robustness of the results, even considering the small difference in QALYs between the compared regimens.

It was necessary to make some assumptions when developing this economic analysis and these were based on the clinical experience of GDG members with aim to reflect current medical practice. The assessment schedule assumptions used to calculate the staff time cost were based on schedules used in the clinical studies and in a selection of hospitals in England and Wales. For the base-case analyses, determining the assessment schedule for fixed-dosing regimen was straight forward as all protocols proposed were similar. As there was variability in the assessment schedules in the symptom-triggered protocols used in the clinical trials, agreeing the frequency of monitoring to use in the base case was more problematic. The commonly used assessment schedule in the Addenbrooke's Hospital (Cambridge) is every hour for 6 hours, then every 2 hours for 18 hours, then every four hours; in the Huntercombe Centre (Sunderland), 10 assessments in the first 24 hours and then 4 hourly; and in the Royal Liverpool and Broadgreen University Hospital Trust, every hour for 12 hours then every 4 hours. The latter was used in base-case analyses and is considered to be the most conservative (i.e. least favourable to the symptom-triggered dosing regimen). The Huntercombe Centre regimen was used in the scenario favouring symptom-triggered option (Table 7) in the deterministic sensitivity analysis. The scenario favouring the fixed-dosing regimen (Table 7) is a hypothetical scenario that uses an increased number of assessments than what we believe would be usual for current practice. Even in this scenario, the symptom-triggered dosing regimen remains cost-effective.

The results of the analysis conducted on patients admitted for a co-morbid condition are sensitive to how long a health-care worker spends with a patient each assessment. If the health-care worker spends longer than 4 minutes extra per assessment using the symptom-triggered regimen compared to using the fixed-dosing regimen, then the symptom-triggered option is no longer cost-effective. While it is unlikely that a competent nurse would ever spend longer than 5 minutes on each assessment, this highlights the need for effective training prior to implementing the symptom-triggered regimen in a service.

The cost of training nurses and implementing the symptom-triggered regimen was marginal and removing this cost did not affect the results of the analyses.

10. Conclusion

The symptom-triggered dosing regimens of benzodiazepines or clomethiazole are cost-effective compared to fixed-dosing regimens in NHS hospitals. This held true for patients admitted for AAW and those admitted for a co-morbid condition.

11. Acknowledgment

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A.4. HEALTH ECONOMIC ANALYSIS – SURGERY VS ENDOSCOPY FOR CHRONIC PANCREATITIS

1. Background

Chronic pancreatitis is a progressive inflammatory disorder, that can cause abdominal pain, various local complications, and endocrine-exocrine pancreatic insufficiency. It is often alcohol-related. When chronic pancreatitis is associated with an obstructed pancreatic duct, a suitable therapy is ductal decompression, using an endoscopic or a surgical approach.

In current medical practice in England and Wales, surgical and endoscopic interventions are available for patients with chronic pancreatitis and an obstructed pancreatic duct. When the disease is associated with alcohol abuse, an intervention is offered to patients whose pain persists despite stopping drinking.

In the literature, after performing a systematic clinical review, two RCTs were found comparing endoscopic and surgical interventions in patients with chronic pancreatitis and an obstructed pancreatic duct[130,131]. The Cahen 2007 study[130] was judged to be of

high quality and the Dite 2003 study[131] was judged to be medium quality[i]. The findings of both RCTs showed that surgical drainage of the pancreatic duct was more effective than endoscopic drainage.

2. Objective

The objective of this economic analysis was to assess the cost-effectiveness of the surgical drainage of the pancreatic duct compared to the endoscopic drainage, for patients with chronic pancreatitis and an obstructed pancreatic duct in England and Wales.

3. Model

This economic analysis was conducted mainly based on the Cahen 2007 study[130], from an England and Wales NHS perspective, and over a 24-month time horizon for the base-case analysis. A lifetime horizon was used in the sensitivity analysis. The health outcome considered was Quality-Adjusted Life Year (QALY). An annual discount rate of 3.5% was applied to both costs and health outcomes incurred after one year.

A 24-month time horizon was chosen for the base-case analysis because this was the median follow-up time in the Cahen trial, and it was judged to illustrate the difference in economic and health outcomes between the interventions that were compared. In addition, extrapolating the Cahen results for time-periods greater than 24 months would involve many assumptions and uncertainties. There were no deaths related to the interventions in either the Cahen 2007[130] or the Dite 2003[131] RCTs. Nevertheless, mortality rates were assigned to the surgical procedure in sensitivity analyses (conducted on the Cahen within-trial time horizon and on a lifetime horizon).

4. Clinical study

The Cahen 2007 RCT[130] was conducted in patients recruited from the Academic Medical Centre in Amsterdam and was carried out between January 2000 and October 2004. All symptomatic patients with chronic pancreatitis and a distal obstruction of the pancreatic duct (without an inflammatory mass) were eligible to participate. Thirty-nine patients underwent randomisation: 19 to endoscopic transampullary drainage of the pancreatic duct; and 20 to operative pancreaticojejunostomy. The baseline demographic and clinical characteristics of patients in the two treatment groups were similar, with the exception of ongoing alcohol abuse (n=5 in the surgical cohort; n=0 in the endoscopic cohort; p=0.05). The most common cause of chronic pancreatitis was alcohol abuse in both treatment groups (60% in the surgical cohort; 47% in the endoscopic cohort). Chronic pancreatitis was associated with complex pathologic features in the studied population (combination of stricture and stones in 79% of patients). The study was ended by the safety committee after an interim analysis on the basis of a significant difference in outcomes. At this time, seven patients had not completed the planned follow-up period of 24 months. The median follow-up time was 24 months (6-24) for both cohorts.

[i] Underpowered; Partly randomised; Baseline characteristics were not reported. This is unclear if groups were similar at baseline. This is unclear if the effect sizes were adjusted for confounding variables.

The endoscopic drainage involved sphincterotomy, dilation of strictures, and removal of stones. The endoscopic procedure was preceded by lithotripsy when one or more intraductal stones (more than 7mm in diameter) were identified by imaging studies. For the surgical cohort, a pancreaticojejunostomy was performed by the method of Partington and Rochelle. The Whipple and Frey procedures were considered for specific disease presentations.

5. Health outcomes

Results of the Cahen 2007 study[130] showed that, in patients with chronic pancreatitis and an obstructed pancreatic duct, surgical drainage was more effective than endoscopic drainage during 24 months of follow-up (Table 1). In addition, the benefits of surgery were demonstrated by more rapid, effective, and sustained pain relief. Finally, one death was reported in the endoscopy group, which was not related to the intervention.

Table 1

Health outcomes – Cahen 2007 trial[130]			
	Endoscopy group	**Surgery group**	**p-value 95% CI**
Izbicki pain score* (mean)	51±23	25±15	<0.001 11 to 36
Pain relief**	32%	75%	0.007 -72 to -15
Technical success	53%	100%	<0.001 -70 to -25
SF-36 – Physical health component	38±9	47±7	0.003 -13 to -3
SF-36 – Mental health component	40±9	45±9	0.15 -8 to 1

* 0-100 scale; higher score = higher pain.

** Benefits of surgery were demonstrated by more rapid, effective, and sustained pain relief.

6. QALYs

In the Cahen study[130], the EQ-5D questionnaire was completed by patients (unpublished). Data were collected for each arm at baseline, six weeks, three months, six months, 12 months, 18 months, and 24 months. We obtained the patient-level EQ-5D data from the trial and generated utility scores for both arms at every follow-up point using the UK tariff. As the baseline utility scores differed slightly between arms (0.335 versus 0.275), we controlled for utility score at baseline by applying linear regression. Utility scores for both arms at every follow-up period are presented in Table 2.

Table 2

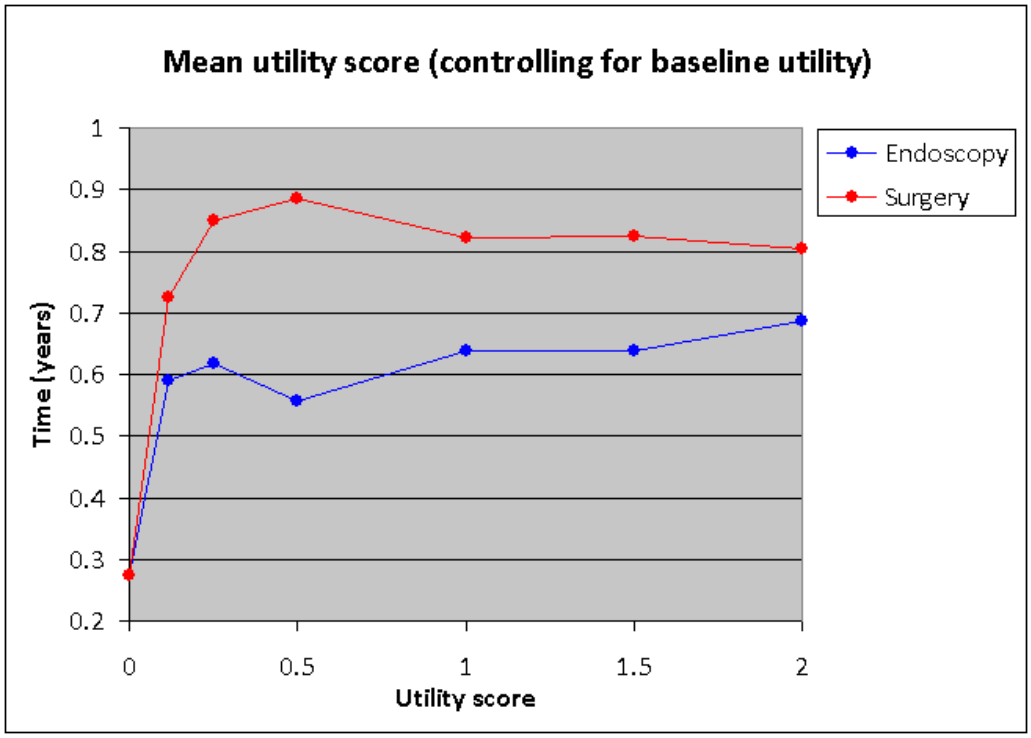
Utility scores			
	Endoscopy	**Surgery-Endoscopy***	**Surgery**
Baseline	0.275 (SE=0.073, n=18)	0	0.275 (SE=0.069, n=19)
6 weeks	0.590 (SE=0.059, n=17)	0.136 (SE=0.09)	0.726 (SE=0.065, n=17)
3 months	0.618 (SE=0.064, n=17)	0.233 (SE=0.072)	0.851 (SE=0.031, n=18)
6 months	0.557 (SE=0.078, n=18)	0.328 (SE=0.091)	0.885 (SE=0.045, n=20)
12 months	0.639 (SE=0.052, n=15)	0.183 (SE=0.068)	0.822 (SE=0.038, n=19)

18 months	0.638 (SE=0.093, n=13)	0.186 (SE=0.096)	0.824 (SE=0.037, n=15)
24 months	0.686 (SE=0.062, n=13)	0.118 (SE=0.083)	0.804 (SE=0.052, n=17)

* Controlling for baseline utility

We used the utility scores presented in Table 2 to calculate QALYs (utility score * time-period) for the 24-month duration of the trial for the base-case analysis, and a lifetime horizon in sensitivity analyses (Section 7.7). For the 24-month time horizon, the QALY difference between the surgery and the endoscopy groups was the area between the curves presented in Figure 1, and was calculated to be 0.40 (1.63 [surgery] – 1.23 [endoscopy]). When discounting at 3.5% utility scores at 18 and 24 months, the QALY difference between arms at 24 months was 0.39 (1.60 [surgery] – 1.21 [endoscopy]).

Figure 1



As discussed in Section 7.7, in sensitivity analyses we applied mortality rates of 1.1% and 2% to patients in the surgery group and to patients who converted to surgery in the endoscopy group. We did this first measuring QALYs within the trial time horizon (24 months), and we repeated this with a lifetime horizon (Section 7.7). For the lifetime horizon, we assumed, post-trial, a constant utility score for the endoscopy group (using the value at 24 months). We assumed no difference in utility score post-trial between the cohorts and therefore applied the constant utility score of the endoscopy group (value at 24 months) to the surgical cohort. For the surgery group, mortality rates were added at the six weeks follow-up[j]. For the endoscopy group, we applied morality rates at 12-months post randomisation[k].

[j] The surgery was performed within 4 weeks after randomisation in the Cahen 2007 trial[130]; From expert judgement, if a patient dies from complications related to surgery, this will typically occur within the first 30 days; and 30-day mortality is usually reported in surgical series.

[k] Common endoscopic methodology is to change stents every 3 months for up to 12 months.

7. Resource use

Outcomes reported by Cahen 2007[130] involving resource use are presented in Table 3.

Table 3

Resource use – Cahen trial[130]			
Outcome	**Endoscopy N=19**	**Surgery N=20**	**Endoscopy vs Surgery 95% CI / p-value**
Procedures (diagnostic and therapeutic) – median (range)	8 (1-21)	3 (1-9)	5 (2 to 8) / < 0.001
Therapeutic procedures – median (range) *	5 (1-11)	1 (1-5)	
Diagnostic procedures – median (range)	3 (0-11)	2 (0-8)	
Hospital stay – median of days (range)	8 (0-128)	11 (5-59)	-3 (-9 to 4) / 0.13
Complications (total) – no. (%)	11 (58)	7 (35)	23% (-8% to 53%) / 0.15
Minor complications – no. (%)	11 (58)	6 (30)	
Major complications – no. (%)	0	1 (5)	
Exocrine function			p=0.05
Insufficiency persisted – no. (%)	11 (61)	13 (65)	
Insufficiency developed – no. (%)	6 (33)	1(5)	
Insufficiency resolved – no. (%)	1 (6)	3 (15)	
Sufficiency persisted – no. (%)	0	3 (15)	
Endocrine function			p=0.48
Insufficiency persisted – no. (%)	3 (17)	4 (20)	
Insufficiency developed – no. (%)	3 (17)	1 (5)	
Insufficiency resolved – no. (%)	1 (6)	0	
Sufficiency persisted – no. (%)	11 (60)	15 (75)	
Conversion to surgery	4 (21)	NA	

* The number of therapeutic interventions reported for the two treatment groups encompassed all endoscopic and surgical therapeutic procedures (including the initial one), endoscopic ultrasonography-guided nerve blockage, and placement of jejunal feeding tube.

7.1 Therapeutic interventions

The number of therapeutic interventions reported for the two treatment groups encompassed all endoscopic and surgical therapeutic procedures, endoscopic ultrasonography-guided nerve blockage, and placement of jejunal feeding tube.

For the endoscopy group (n=19), the Cahen study[130] reported a median of five interventions per patient. The Dite 2003 RCT[131] is in agreement with Cahen 2007, reporting a mean of 5.15 endoscopic interventions per patients[l]. In our analysis, we costed five endoscopic interventions per patient in the endoscopy group (Table 4).

In the Cahen 2007 trial[130], 16 patients in the endoscopy group were referred for lithotripsy treatment before attending the endoscopic procedure: ten patients received one session; and six patients received multiple sessions (median of 1 [1 to 5]). In our analysis, we assumed that ten patients received one session, and six patients received two sessions (Table 4). In the Cahen 2007 trial, for patients attending a lithotripsy

[l] 48% of patients received a mean of two initial interventions (sphincterotomy); and 52% received a mean of two initial interventions plus a mean of six stent exchanges during a 5-year follow-up period[131].

session before an endoscopic procedure, a general anaesthesia with propofol was administered. For patients not requiring a lithotripsy session, endoscopic procedures were performed under conscious sedation. No additional cost was added for patients requiring a general anaesthesia with propofol and we assumed that the cost of anaesthesia / sedation was already included in the therapeutic procedure cost.

For the surgery group (n=20), Cahen reported a median of one intervention per patient. Eighteen patients underwent a pancreaticojejunostomy, one patient a Whipple procedure, and one patient a Frey procedure. We costed 18 pancreaticojejunostomy, one Whipple procedure, and one Frey procedure (Table 4).

Table 4

Therapeutic procedure			
Procedure	**HRG-code classification**	**Mean unit cost**	**Mean length of stay**
Endoscopic intervention	Endoscopic Retrograde Cholangiopancreatography category 2 with a length of stay of 2 days or less	£739	1 day
Extracorporeal shockwave lithotripsy of calculus of pancreas	Endoscopic/Radiology category 2 without complications	£1,394	3 days
pancreaticojejunostomy	Hepatobiliary Procedures category 5 with complications	£6,024	10 days
Frey procedure	Hepatobiliary Procedures category 5 with complications	£6,024	10 days
Wipple procedure	Hepatobiliary Procedures category 7	£7,697	13 days
Laparotomy intervention	Hepatobiliary Procedure category 5 without complication	£5,528	8 days

Source: *National Schedule of Reference Costs 2006-07*[97]

7.2 Diagnostic procedures

The Cahen paper[130] discussed the use of 'Magnetic resonance cholangiopancreatography' and 'Contrast-enhanced computed tomography' for diagnostic assessments. The study reported a median of two diagnostic procedures in the surgery group and of three in the endoscopy group. The cost for these diagnostic procedures in England and Wales are presented in the Table 5.

Table 5

Diagnostic procedure		
Diagnostic procedures	**Inpatient cost**	**Outpatient cost**
Computed Tomography Scan, 2 areas, with contrast	£121	£125
Magnetic Resonance Imaging Scan, one area, no contrast	£228	£198

Source: *National Schedule of Reference Costs 2006-07*[97]

For the base-case analysis we costed 50% of the diagnostic interventions as 'Magnetic Resonance Imaging Scan, one area, no contrast', and 50% as 'Computed Tomography Scan, 2 areas, with contrast'. These interventions were costed as an inpatient procedure for the first assessment in both cohorts, and as an outpatient procedure for the second assessment in the surgical cohort and for the second and third assessments in the endoscopic cohort.

We also conducted two one-way sensitivity analyses: one assuming all tests were CT scans the other assuming all were MRIs.

7.3 Complications

For the endoscopy group, 18 minor complications were reported in 11 patients: one patient suffered a skin wound caused by the shock-wave lithotripsy; five patients had stent complications which involved stent replacement; four patients developed pancreatitis; and one patient developed cholecystitis. For the base-case analysis, it was considered that 26% of patients in the endoscopy arm would need a further endoscopic intervention for treating stent-related complications (Table 4). The treatment of the skin wound was not costed as it was taken to be an unusual complication of the lithotripsy intervention. The cost of treatments for pancreatitis and cholecystitis were not included as we assumed that these treatment costs would be captured within the HRG cost for the main procedure (Section 7.1).

Clinical studies assessing endoscopic drainage for treating patients with chronic pancreatitis were reviewed for stent-related dysfunction/complication rates. Table 6 details results of this review, showing probabilities varying between 8% and 64%. These extreme values were used in the sensitivity analysis.

Table 6

Stent-dysfunctions / Stent-related complications		
Study	**Method**	**Rates for stent-dysfunctions / stent-related complications**
Kowalczyk 2009[181]	• Endoscopic therapy for chronic pancreatitis – Review (non systematic)	10% to 48%
Cremer 1991[182]	• Prospective case series • 37 months follow-up	6/75 (8%)
Smits 1995[183]	• Prospective case series • 34 months follow-up	27/49 (55%)
Cahen 2005[184]	• Retrospective case series • Long-term follow-up (from 1983-2000 to 2002)	13/92 (14%)
Smits 1996[185]	• Retrospective case series • 49 months follow up	37/58 (64%)
Deviere 1990[186]	• Prospective case series • 14-month follow-up	8/23 (35%)
Deviere 1994[187]	• Prospective case series • 33 months follow-up	2/20 (10%)
Barthet 1994[188]	• Retrospective case series • 18 months follow-up	2/19 (11%)
Cahen 2005[189]	• Retrospective case series • 45 months follow-up	28/58 (48%)
Total		123/394 (31%)

For the surgery group, complications were reported in seven patients: one had leakage of the anastomosis, requiring a laparotomy intervention (major complication); two had suspected bleeding which were treated with blood transfusion (minor complication); one patient developed pneumonia (minor complication); and three patients had a wound infection (minor complication). For our analysis, we only considered the laparotomy intervention for treating the leakage of anastomosis in one patient (5%) (Table 4). The cost of treatment for other complications was not included as we assumed that these treatment costs were included in the HRG cost for the main

procedure (Section 7.1). Indeed, in current medical practice, complications from surgery are usually treated in 'post-operative care unit', and these costs ought to be captured within the HRG cost.

Clinical studies assessing surgery for treating patients with chronic pancreatitis were reviewed for reoperation rates. Table 7 details results of this review, showing probabilities varying between 2.6% and 7.1%. These extreme values were used in the sensitivity analysis.

Table 7

Re-operation		
Study	**Method**	**Re-operation rates**
Dite 2003[131]	• RCT • 5 years follow-up	2/76 (2.6%)
Sielezneff 2000[190]	• Retrospective case series • 65 months follow-up	3/57 (5.3%)
Adams 1994[191]	• Prospective case series • 6.3 years follow-up	6/84 (7.1%)
Lucas 1999[192]	• Prospective case series • 36.1 months follow-up	6/122 (4.9%)
Total		17/339 (5.0%)

7.4 Length of hospital stay

The total length of hospital stay was reported to be a median of eight days for the endoscopy group, and a median of 11 days for the surgery group.

A number of inpatient bed-days was already included in the therapeutic interventions cost (surgery, endoscopy, and lithotripsy), and in the cost of treating complications. The total number of inpatient bed-days was 206 for the endoscopic cohort (N=19) and 211 for the surgical cohort (N=20). Using the median total length of hospital stay per patient reported by Cahen 2007[130] of eight days for the endoscopy group and of 11 days for the surgery group, the total inpatient bed-day for each cohort was calculated to be 152 days for the endoscopic cohort and 220 days for the surgical cohort. It shows that, using the number of inpatient bed-days proposed by the *National Schedule of Reference Costs 2006-07*[97] (included in the therapeutic interventions cost and in the treatment of complications cost), seems to have resulted in overestimating the length of hospital stay for the endoscopic cohort and underestimating the length of hospital stay for the surgical cohort.

A sensitivity analysis was performed to vary the length of hospital stay, increasing the cohort-number of inpatient bed-days for the surgery group by nine days, and reducing the endoscopy group inpatient bed-days by 54 days. Using the mean cost per inpatient bed-day for the surgical and the endoscopic procedures of £185.50[m], we adjusted the hospitalisation cost removing £527.21 per patient from the endoscopy group, and adding £83.48 per patient to the surgery group.

7.5 Pancreas function

[m] £104 per inpatient bed-day for the endoscopic procedure ('Elective Inpatient Excess Bed Day – Endoscopic Retrograde Cholangiopancreatography category 2 with a length of stay of 2 days or less') and £267 for the surgical intervention ('Elective Inpatient Excess Bed Day – Hepatobiliary Procedures category 5 with complications')[97].

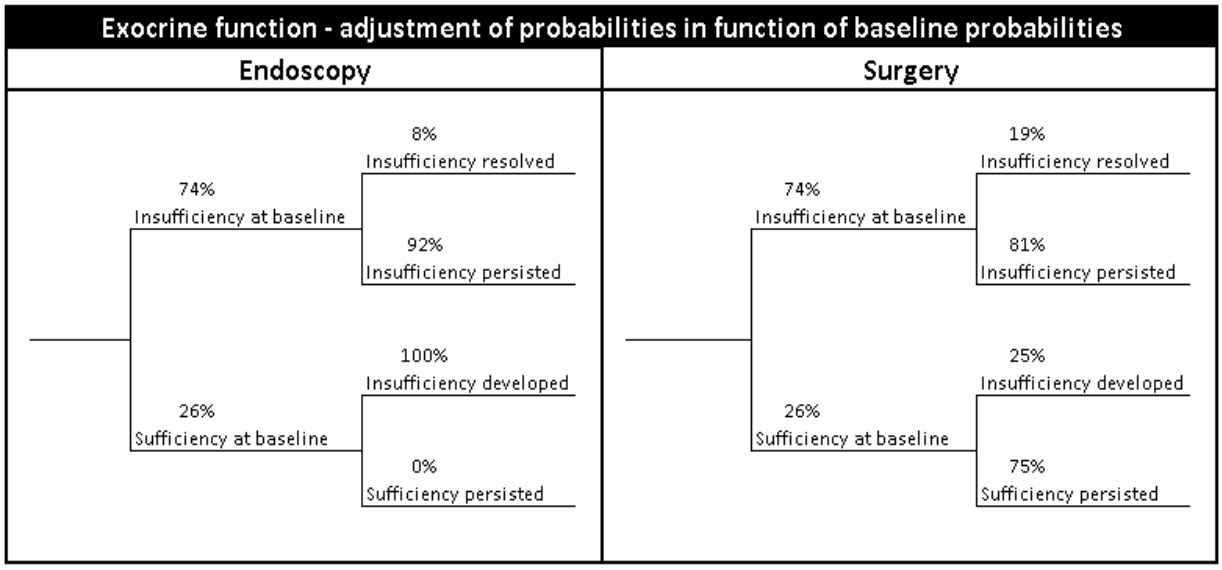
Outcomes on exocrine function from the Cahen 2007 trial[130] are presented in Table 3. The difference in effect of interventions on the exocrine function status between groups was non-significant (p=0.05). However, due to a marginal trend toward significance and to the high cost of the drug therapy, it was decided to cost the treatment of exocrine insufficiency.

We adjusted the baseline rate of exocrine insufficiency to be the same in each arm (Table 8 and Figure 2). Probabilities used for our analysis are presented in Table 9.

Table 8

Exocrine function			
	Endoscopy	**Surgery**	**Combined**
Insufficiency at baseline	12/18=67%	16/20=80%	28/38=74%
Insufficiency resolved / insufficient at baseline	1/12=8%	3/16=19%	N/A
Insufficiency developed / Sufficient at baseline	6/6=100%	1/4=25%	N/A

Figure 2



Notes: (1) The probabilities of sufficiency/insufficiency at baseline are counting patients of the surgical and the endoscopic cohorts; (2) n=20 for surgery group, n=18 for endoscopy group (results were not reported for one patient in the endoscopy group) – Table 3; (3) The second tier of both algorithms are presenting probabilities related to the surgical cohort or the endoscopic cohort alone.

Table 9

Adjusted exocrine function probabilities		
Exocrine function status	**Endoscopy**	**Surgery**
Insufficiency resolved	74%*8% = 6%	74%*19% = 14%
Insufficiency persisted	74%*92% = 68%	74%*81% = 60%
Insufficiency developed	26%*100% = 26%	26%*25% = 7%
Sufficiency persisted	26%*0% = 0%	26%*75% = 20%

The treatment of exocrine insufficiency with pancreatic enzyme supplementations was calculated for two years in patients whose insufficiency persisted, and for one year in patients whose insufficiency developed or resolved. This treatment was costed as eight capsules a day of Creon 10000 (Creon is widely used in current practice in England and

Wales). The 10000 formulation (as compared with 25000) was chosen, being a conservative decision (Table 10).

Table 10

Exocrine insufficiency – Treatment cost			
Drug	**Cost per pack**	**Unit per pack**	**Cost per year (8 capsules a day)**
Creon® 10 000	£16.66	100	£486.47

Source: *BNF No. 57 (March 2009)*[117]

In the Cahen 2007 trial[130], the difference between groups for the effect of the interventions on the endocrine function status was non-significant (p=0.48) (Table 3). This is in agreement with the Dite 2003 RCT[131], which reported non-significant probabilities for developing diabetes (new onset) between the surgical and the endoscopic cohorts at five years follow-up. Therefore, the treatment for endocrine insufficiency was not costed in our analysis.

7.6 Conversion to surgery

In the Cahen study[130], four patients converted to surgery as the endoscopic treatment was considered to have failed (21%). A pancreaticojejunostomy was costed for these four patients (Table 4).

Clinical studies assessing endoscopic drainage for treating patients with chronic pancreatitis were reviewed for rates of conversion to surgery. Table 11 details results of this review, showing probabilities varying between 0% and 28%. These extreme values were used in the sensitivity analysis.

Table 11

Patients needing surgery after undergoing endoscopic drainage		
Study	**Method**	**Rates of patients undergoing surgery**
Kowalczyk 2009[181]	• Endoscopic therapy for chronic pancreatitis – Review (non systematic)	4% to 24%
Dite 2003[131]	• RCT (endoscopy group n=64) • 5 years follow-up	0/64 (0%)
Rosch 2002[193]	• Prospective case series • 4.9 years follow-up	238/1018 (23%)
Binmoeller 1995[194]	• Prospective case series • 9 years follow-up	22/93 (24%)
Cahen 2005[184]	• Retrospective case series • Long-term follow-up (from 1983-2000 to 2002)	8/92 (9%)
Smits 1996[185]	• Retrospective case series • 49 months follow up	16/58 (28%)
Barthet 1994[188]	• Prospective case series • 33 months follow-up	4/19 (21%)
Total		288/1344 (21%)

7.7 Mortality

Cahen 2007[130] and Dite 2003[131] RCTs reported no deaths related to the interventions. No mortality was considered in the base-case analysis. From a review of clinical studies

(Table 12), the mortality related to surgical drainage was estimated to be 1.1%[n]. It was decided to use a mortality rate related to surgery of 1.1% and an upper estimate of 2% in the sensitivity analysis. These mortality rates were applied to patients in the surgery group and to patients who converted to surgery in the endoscopy group.

We conducted sensitivity analyses using mortality rates of 1.1% and 2% for surgical drainage. We did this first measuring QALYs within the trial time horizon (24 months). We repeated this sensitivity analysis with a lifetime horizon. When based on a lifetime horizon, we assumed, post-trial, no difference between cohorts in the yearly cost for treating patients. The yearly cost per patient post-trial is presented in Section 8. In addition for the lifetime horizon analyses, we assumed, post-trial, a constant utility score for the endoscopy group (using the value at 24 months). We assumed no difference in utility score post-trial between the cohorts and therefore applied the constant utility score of the endoscopy group (value at 24 months) to the surgical cohort.

According to a review from Bornman 2001[195], the life expectancy for patients with advanced chronic pancreatitis is typically shortened by 10-20 years. In the Cahen 2007 trial[130], patients had chronic pancreatitis associated with complex pathologic features (combination of stricture and stone in 79% of patients). The mean age was 46±12 years for the surgery group and this cohort included 75% males. Using the male UK life expectancy of 77 years[196], considering that the life expectancy for patients with chronic pancreatitis is shortened by 15 years and that patients are attending surgery at 46 years old, the life expectancy to use was estimated to be 16 years. This life expectancy was used for both the surgery and the endoscopy groups.

Table 12

Mortality related to surgery for chronic pancreatitis		
Study	**Method**	**Mortality**
Cahen 2007[130]	• RCT • 2 years follow-up • 20 patients in the surgery group	• No death
Dite 2003[131]	• RCT • 5 years follow-up • 76 patients in the surgery group	• No death
Schnelldorfer 2008[197]	• Prospective cohort study • 5.5 years follow-up • 171 patients	• Overall perioperative mortality rate of 2%
Lucas 1999[192]	• Prospective case series • 36.1 months follow-up • 124 patients	• 2 patients died *
Schnelldorfer 2003[198]	• Retrospective cohort study • Records of patients from 1995 through 2001 were reviewed • 21 with chronic pancreatitis associated with pancreas divisum • 108 with chronic pancreatitis associated with other aetiologies	• 0/21 patient died in pancreas divisum group • 2/108 died in the other group **
Adams 1994[191]	• Prospective case series • 6.3 years follow-up	• No patient died in the 30 days following the surgery

[n] The mortality rate of 1.1% related to surgical drainage was calculated dividing the total number of deaths related to surgery by the total number of patients attending a surgery in the reviewed clinical studies.

	• 85 patients	
Kalady 2001[199]	• Retrospective case series • 38 months follow-up • 60 patients	• No death
Sielezneff 2000[190]	• Retrospective case series • 65 months follow-up • 57 patients	• No death
Terrace 2007[200]	• Retrospective cohort study • 30 months follow-up • 50 patients	• 2 patients died during the 30-days period following the surgery ¥
Madura 2003[201]	• Prospective case series • Last follow-up visit at 1 year • 35 patients	• No operative death
Rios 1998[202]	• Retrospective case series • 10.3 months follow-up • 17 patients	• No death

* One patient died of an unrecognized oesophageal perforation during intubation and the other of leakage of one-layer pancreaticojejunostomy (after a DuVal procedure and a Thal procedure).
** The first patient was on perioperative immunosuppressive therapy for a cadaveric renal transplant and systemic lupus erythematosus with end-stage renal disease. The second case was a patient with poorly controlled diabetes mellitus with end-stage renal disease, history of alcohol abuse, and severe coronary artery disease. Both patients had spontaneous dehiscence of the pancreatic anastomosis leading to sepsis and, consequently, death.
¥ One patient died following a post-operative myocardial infarction; and one patient sustained Roux-limb infarction leading to sepsis, multi-organ failure and death.

8. Costs post-trial

The yearly cost applied to patients in both the surgery and endoscopy groups after 24-months was extrapolated from the observed resource usage from the trial (Table 13). This cost was estimated to be £1 866. Table 13 presents how was calculated this cost.

Table 13

Yearly cost for treating patients with chronic pancreatitis (post-trial)				
Cost component	**Estimate**	**Unit cost**	**Yearly cost**	**Rational**
Diagnostic procedure (nb)	1	£125*	£125	▪ We assumed an average of one outpatient CT-Scan visit per patient per year
Hospitalisation (days)	4	£185.50*	£742	▪ The number of inpatient days was taken from the endoscopic cohort in the Cahen trial (8 for 24 months) ▪ We used the mean cost per inpatient bed-day for the surgical and the endoscopic procedures** ▪ We used data from the endoscopy group to be consistent with the previous assumption that, post-trial, the constant utility score applied to the endoscopy group (value at 24 months for endoscopy) was also applied to the surgical cohort (Section 7.7)
Exocrine dysfunction				
Insufficiency persisted (%)	68%	486.47¥	£330.80	▪ Data were taken from the endoscopic cohort in the Cahen trial and adjusted with the baseline characteristics of the surgical cohort (Section 7.5) ▪ We assumed that patients were taking Creon

				10000 as enzyme supplementation. The yearly cost is presented ▪ We used data from the endoscopic cohort for the reason explained above
Insufficiency developed (%)	26%	486.47¥	£126.48	▪ Same as for 'Insufficiency persisted' above
Endocrine dysfunction				
Insufficiency persisted (%)	16%	£284.70¥	£45.55	▪ Data were taken from the endoscopic cohort in the Cahen trial and adjusted with the baseline characteristics of the surgical cohort (adjusted in the same way as presented for exocrine dysfunction in Section 7.5) ▪ We costed a long-acting recombinant human insulin analogue ('Insulin Detemir') as 30 units per day (in two divided doses) ▪ We used data from the endoscopic cohort for the reason explained above
Insufficiency developed (%)	17%	£284.70¥	£48.40	▪ Same as for 'Insufficiency persisted' above
Outpatient visit (nb)	4	£89*	£356	▪ We assumed four outpatient visit per year to reflect current practice ▪ The cost was taken from the NHS reference cost database: 'Consultant Led Follow up Attendance Outpatient, Hepatobiliary & Pancreatic Surgery'[97]
Analgesic use				
Opiate (%)	14%	£528.28¥	£73.96	▪ Data were taken from a UK retrospective cohort study (Terrace 2007[200]), assessing patients attending a pancreaticojejunostomy. The data presented are post surgery (all patients were on analgesic treatment before surgery) ▪ We assumed that 80% of patients was taking 400mg/day of oral tramadol, and 20% of patients was using fentanyl patches releasing 75 micrograms/hour for 72 hours. The yearly cost is presented.
Non-opiate (%)	39%	£45.55¥	£17.76	▪ Data were taken from the Terrace 2007 study[200] ▪ We costed 4g of paracetamol daily. The yearly cost is presented.
Total			£1865.95	

* Source: *NHS reference cost* [97].
** £104 per inpatient bed-day for the endoscopic procedure ('Elective Inpatient Excess Bed Day – Endoscopic Retrograde Cholangiopancreatography category 2 with a length of stay of 2 days or less') and £267 for the surgical intervention ('Elective Inpatient Excess Bed Day – Hepatobiliary Procedures category 5 with complications')[97].
¥ Source: *BNF No. 57 (March 2009)*[117]

9. Sensitivity analysis

Sensitivity analyses were performed to assess the robustness of the results to plausible variations in the model parameters. Five one-way sensitivity analyses were conducted, varying one parameter at a time from the base case: two were costing differently the diagnostic procedures (Section 7.2); two were varying the ratio of patients who convert to surgery after failure of the endoscopic treatment (Section 7.6); and one varied the

length of hospital stay (Section 7.4). In addition, two-way sensitivity analyses were performed, concurrently using two extreme varying estimates: the probability of stent-related complication (endoscopy group – Section 7.3) and the rate of re-operation (surgery group – Section 7.3). Four combinations were assessed. Finally, sensitivity analyses were conducted applying mortality rates to surgical drainage on the Cahen within-trial time horizon (24 months) and on a lifetime horizon (Section 7.7).

10. Probabilistic analysis

This economic analysis presents probabilistic results. A probabilistic analysis applies probability distributions for model parameters and presents the empirical distribution of the cost-effectiveness results. A gamma distribution was applied to cost estimates (bounded at 0). A beta distribution was applied to probability estimates and to utility scores (bounded between 0 and 1) (Table 14) Results of the base-case analysis and of the sensitivity analyses were re-calculated 5000 times, with all of the model parameters set simultaneously, selected at random from the respective parameter distribution. Results presented are the mean of the 5000 computed simulations.

Table 14

Parameters used in the probabilistic sensitivity analysis				
Description of variable	**Mean value**	**Probability distribution**	**Parameters**	**Source**
Cost units estimates				
Endoscopic intervention (therapeutic & for treating complications)	£739 SE = 483	Gamma	α = 2.34 β = 316.11 Using interquartile range* (£402 - £1,054)	National Schedule of Reference Costs 2006-07[97]
Lithotripsy treatment	£1,394 SE = 880	Gamma	α = 2.51 β = 555.43 Using interquartile range (£499 - £1,686)	National Schedule of Reference Costs 2006-07[97]
Surgery (pancreaticojejunostomy & Frey)	£6,024 SE = 2580	Gamma	α = 5.45 β = 1104.75 Using interquartile range (£2,867 - £6,347)	National Schedule of Reference Costs 2006-07[97]
Surgery (Wipple)	£7,697 SE = 4419	Gamma	α = 3.03 β = 2536.92 Using interquartile range (£4,710 - £10,671)	National Schedule of Reference Costs 2006-07[97]
Surgery (for treating complications post-surgery / repeated surgery)	£5,528 SE = 2837	Gamma	α = 3.80 β = 1455.92 Using interquartile range (£2,273 - £6,100)	National Schedule of Reference Costs 2006-07[97]
CT-Scan / Inpatient	£121 SE = 59	Gamma	α = 4.16 β = 29.07 Using interquartile range (£78 - £158)	National Schedule of Reference Costs 2006-07[97]
CT-Scan / Outpatient	£125 SE = 63	Gamma	α = 3.94 β = 31.76 Using interquartile range (£75 - £160)	National Schedule of Reference Costs 2006-07[97]
MRI / Inpatient	£228 SE = 128	Gamma	α = 3.16 β = 72.14	National Schedule of Reference Costs

			Using interquartile range (£121 - £294)	2006-07[97]
MRI / Outpatient	£198 SE = 115	Gamma	α = 2.97 β = 66.68 Using interquartile range (£116 - £271)	National Schedule of Reference Costs 2006-07[97]
Inpatient bed-day - Endoscopic	£104 SE = 121	Gamma	α = 0.74 β = 140.39 Using interquartile range (£130 - £293)	National Schedule of Reference Costs 2006-07[97]
Inpatient bed-day - Surgery	£267 SE = 68	Gamma	α = 15.33 β = 17.42 Using interquartile range (£167 - £259)	National Schedule of Reference Costs 2006-07[97]
Outpatient visit	£89 SE = 13	Gamma	α = 44.49 β = 2.00 Using interquartile range (£87 - £105)	National Schedule of Reference Costs 2006-07[97]
Probability estimates				
Stent-related complications / base case	5/19 (26%)	Beta	α = 5 β = 14	Cahen 2007[130]
Stent-related complications / sensitivity analyses using lower estimate	6/75 (8%)	Beta	α = 6 β = 69	Cremer 1991[182]
Stent-related complications / sensitivity analyses using higher estimate	37/58 (64%)	Beta	α = 37 β = 21	Smits 1996[185]
Re-operation post surgery / base case	1/20 (5%)	Beta	α = 1 β = 19	Cahen 2007[130]
Re-operation post surgery / sensitivity analyses using lower estimate	2/76 (2.6%)	Beta	α = 2 β = 74	Dite 2003[131]
Re-operation post surgery / sensitivity analyses using higher estimate	6/84 (7.1%)	Beta	α = 6 β = 116	Adam 1994[191]
Surgery post-endoscopy / base case	4/19 (21%)	Beta	α = 4 β = 15	Cahen 2007[130]
Surgery post-endoscopy / sensitivity analysis using higher estimate	16/58 (28%)	Beta	α = 16 β = 42	Smits 1996[185]
Exocrine function (see figure 1)				
Insufficiency at baseline	28/38	Beta	α = 28 β = 10	Cahen 2007[130]
Insufficiency resolved – Surgery group	3/16	Beta	α = 3 β = 13	Cahen 2007[130]
Insufficiency resolved – Endoscopy group	1/12	Beta	α = 1 β = 11	Cahen 2007[130]

Insufficiency developed – Surgery group**	1/4	Beta	α = 1 β = 3	Cahen 2007[130]
Endocrine function				
Insufficiency at baseline	8/38 (21%)	Beta	α = 8 β = 30	Cahen 2007[130]
Insufficiency resolved – Endoscopy group¥	1/4 (25%)	Beta	α = 1 β = 3	Cahen 2007[130]
Insufficiency developed – Surgery group	1/16 (6%)	Beta	α = 1 β = 15	Cahen 2007[130]
Insufficiency developed – Endoscopy group	3/14 (21%)	Beta	α = 3 β = 11	Cahen 2007[130]
Surgical mortality	9.42/824 (1.1%)	Beta	α = 9.42 β = 814.58	Clinical review (Table 10)
Opiate use	4/28 (14%)	Beta	α = 4 β = 24	Terrace 2007[200]
Non-opiate use	11/28 (39%)	Beta	α = 11 β = 17	Terrace 2007[200]
Utility scores				
Difference between cohorts at 6 weeks controlling for baseline utility	0.136 SE = 0.090	Beta	α = 1.97 β = 12.53	Unpublished data from Cahen 2007[130]
Difference between cohorts at 3 months controlling for baseline utility	0.233 SE = 0.072	Beta	α = 8.03 β = 26.44	Unpublished data from Cahen 2007[130]
Difference between cohorts at 6 months controlling for baseline utility	0.328 SE = 0.091	Beta	α = 8.73 β = 17.89	Unpublished data from Cahen 2007[130]
Difference between cohorts at 12 months controlling for baseline utility	0.183 SE = 0.068	Beta	α = 5.92 β = 26.42	Unpublished data from Cahen 2007[130]
Difference between cohorts at 18 months controlling for baseline utility	0.186 SE = 0.096	Beta	α = 3.06 β = 13.37	Unpublished data from Cahen 2007[130]
Difference between cohorts at 24 months controlling for baseline utility	0.118 SE = 0.083	Beta	α = 1.78 β = 13.32	Unpublished data from Cahen 2007[130]

*We used the interquartile range (IQR) to approximately estimate the SE of the mean using the following equation: $se=0.5xIQR / Z_{0.75}$

**This estimate was not varied for the endoscopy group; the probability of sufficiency that persisted in this group was reported to be 0% in the Cahen paper[130] (Table 3).

¥ This estimate was not varied for the surgical group; the probability of insufficiency that resolved in this group was reported to be 0% in the Cahen paper[130].

11. Results

The result of the base-case analysis was that surgical drainage of the pancreatic duct dominates endoscopic drainage (it was more effective and less costly – Table 15). The sensitivity analysis showed that the surgical option remains dominant (cost-saving) in the majority of scenarios (Table 16 and Table 17). The results were most sensitive to the proportion of patients in the endoscopy group who convert to surgical drainage when the endoscopic drainage failed. When patient conversion to surgery was less than 10%, surgical drainage was no longer cost-saving, but it was still highly cost-effective when compared with a threshold of £20,000 per QALY gained (£1,729 per QALY gained when the probability of conversion to surgery was 0% - Table 16). The base-case analysis, the analyses considering mortality rates related to surgical drainage, and all other sensitivity analyses showed very high probabilities of cost-effectiveness for surgical drainage compared to endoscopic drainage. The presented results reveal that surgical drainage is highly cost-effective compared to endoscopic drainage.

Table 15

Base-case analysis probabilistic results: Mean costs		
	Endoscopy	**Surgery**
Therapeutic procedures	£5,328	£6,153
Diagnostic procedures	£501	£339
Complications	£197	£284
Exocrine function	£800	£671
Conversion to surgery	£1,243	n/a
Total	**£8,068**	**£7,446**

Table 16

Probabilistic results					
	Cost Difference (surgery-endoscopy)	**Probability of surgery being cost-saving**	**QALY gained (surgery – endoscopy)**	**Incremental Net Monetary Benefit* (surgery - endoscopy)**	**Probability of surgery being cost-effective***
Base-case analysis	-£622	55.6%	0.39	£8,472	99.1%
Sensitivity analyses considering mortality related to surgery					
1.1% mortality related to surgery – 24-month time horizon	-£622	55.6%	0.38	£8,150	99.0%
2% mortality related to surgery – 24-month time horizon	-£622	55.6%	0.36	£7,911	98.7%
1.1% mortality related to surgery – lifetime horizon	-£828	57.7%	0.31	£7,008	97.5%
2% mortality related to surgery – lifetime horizon	-£969	59.4%	0.25	£5,939	95.5%
Other one-way sensitivity analysis					
Diagnostic procedure - 100% MRI	-£622	55.7%	0.39	£8,483	99.3%
Diagnostic procedure - 100% CT-Scan	-£656	56.4%	0.39	£8,454	99.1%
Lower estimate for conversion to surgery	£676	40.8%	0.39	£7,142	96.5%

post-endoscopy (0%)					
Higher estimate for conversion to surgery post-endoscopy (28%)	-£960	59.5%	0.39	£8,808	99.4%
Length of hospital stay adjustment	-£5	48.0%	0.39	£7,855	98.6%

* Compared with a threshold of £20,000 per QALY gained

Table 17

Two-way sensitivity analysis		**Endoscopic complication rates**	
		Higher (64%)	**Lower (8%)**
Surgical complication rates	**Higher (7.1%)**	-£779* 56.6%** £8,598¥ 99.0%¥¥	-£268 51.1% £8,145 99.1%
	Lower (2.6%)	-£1023 59.0% £8,863 99.3%	-£612 55.1% £8,446 98.9%

* Cost difference (surgery - endoscopy)
** Probability of surgery being cost-saving
¥ Incremental Net Monetary Benefit – £20,000 per QALY gained (surgery - endoscopy)
¥¥ Probability of surgery being cost-effective at £20,000 per QALY gained

12. Discussion

A 24-month time horizon was chosen for the base-case analysis as this was the period covered by the Cahen study[130]. It was judged that extrapolating the results of the Cahen trial would involve uncertainty and that the 24-month time horizon adequately captures the difference in economic and health outcomes between the compared interventions (keeping in mind that these treatments are undertaken for pain-control). The Cahen trial was stopped after an interim analysis on the basis of a significant difference in outcomes favouring surgery. This may have resulted in overestimating the health outcomes in favour of surgery.

The sensitivity analysis varying the probability for conversion to surgery in the endoscopy group showed that surgical drainage was no longer cost-saving when patient conversion to surgery was less than 10%. However, even with a probability of conversion to surgery of 0% surgery was highly cost-effective with a cost of £1,729 per QALY gained.

The sensitivity analysis adjusting the amount of in-patient bed-days from the length of hospital stay included in the HRG-code cost to the amount reported by the Cahen study[130], showed low cost savings for surgery, with the probability that surgery is cost-saving being 48%. However. the probability that surgery is cost-effectiveness for this analysis was 98.6%. The Cahen study[130] was conducted in the Netherlands, a country with a healthcare system and with practices in this area that may be different to the UK NHS. Therefore the base-case analysis using the HRG-code length of hospital stay is perhaps more relevant for estimating the cost impact on the UK NHS.

The sensitivity analysis applying mortality rates of 1.1% and 2% to surgical drainage showed cost-saving results with very high probabilities of cost-effectiveness. Furthermore, the probability that surgery is cost-effectiveness was very high across all analyses, varying from 95.5% to 99.4%.

We have used medians to estimate means for some resource use outcomes, because they were the best available estimates as reported by Cahen 2007[o]. In health economic assessments, the mean is the most informative measure for costing resource use, and provide information about the total cost that will be incurred by treating all patients, which is needed as the basis for healthcare policy decisions. The median in contrast describe a 'typical' cost for an individual[135]. The most costly interventions (surgical and endoscopic therapeutic procedures, and lithotripsy sessions) were costed using median estimates. Although, the mean estimates by Dite 2003[131] for numbers of therapeutic procedures seem to be in agreement with Cahen 2007[130] medians. Moreover, to be safe, we used conservative assumptions not favouring surgical drainage when costing lithotripsy sessions.

Finally, the results of the present study cannot be extrapolated to all patients with ductal obstruction due to chronic pancreatitis because patients with an inflammatory mass were excluded from the Cahen trial[130].

13. Conclusion

Surgical drainage of the pancreatic duct is highly cost-effective compared to endoscopic drainage for treating patients with chronic pancreatitis and an obstructed pancreatic duct from the perspective of the NHS in England and Wales.

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A.5. REFERENCE LIST

1 National Institute for Health and Clinical Excellence. *The Guidelines Manual.* NICE, 2007.

2 National Institute for Health and Clinical Excellence. *The Guidelines Manual.* London: NICE, 2009.

3 NHS Information Centre, Lifestyle Statistics. *Statistics on Alcohol: England, 2009.* UK: Health and Social Care Information Centre, 2009.

[o] Number of surgical and endoscopic therapeutic interventions; number of diagnostic interventions; total length of hospital stay; number of lithotripsy sessions.

4 Pirmohamed M, Brown C, Owens L et al. The burden of alcohol misuse on an inner-city general hospital. *QJM.* 2000; 93(5):291-295.

5 Royal College of Physicians. *Alcohol - can the NHS afford it? Recommendations for a coherent alcohol strategy for hospitals. A report of a working party of the Royal College of Physicians.* Royal College of Physicians, 2001.

6 Caetano R, Clark CL, Tam T. Alcohol consumption among racial/ethnic minorities: theory and research. *Alcohol Health & Research World.* 1998; 22(4):233-241.

7 Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. *Alcoholism: Clinical & Experimental Research.* 2001; 25(8):1181-1187.

8 Lukan JK, Reed DN, Jr., Looney SW et al. Risk factors for delirium tremens in trauma patients. *Journal of Trauma-Injury Infection & Critical Care.* 2002; 53(5):901-906.

9 Duka T, Townshend JM, Collier K et al. Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. *Alcoholism: Clinical & Experimental Research.* 2003; 27(10):1563-1572.

10 Malcolm R, Herron JE, Anton RF et al. Recurrent detoxification may elevate alcohol craving as measured by the Obsessive Compulsive Drinking scale. *Alcohol.* 2000; 20(2):181-185.

11 Schuckit MA, Tipp JE, Reich T et al. The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. *Addiction.* 1995; 90(10):1335-1347.

12 Wetterling T, Driessen M, Kanitz RD et al. The severity of alcohol withdrawal is not age dependent. *Alcohol & Alcoholism.* 2001; 36(1):75-78.

13 Wetterling T, Kanitz RD, Besters B et al. A new rating scale for the assessment of the alcohol-withdrawal syndrome (AWS scale). *Alcohol & Alcoholism.* 1997; 32(6):753-760.

14 Booth BM, Blow FC. The kindling hypothesis: further evidence from a U.S. national study of alcoholic men. *Alcohol & Alcoholism.* 1993; 28(5):593-598.

15 Kraemer KL. The cost-effectiveness and cost-benefit of screening and brief intervention for unhealthy alcohol use in medical settings. *Substance Abuse.* 2007; 28(3):67-77.

16 Lechtenberg R, Worner TM. Relative kindling effect of detoxification and non-detoxification admissions in alcoholics. *Alcohol & Alcoholism.* 1991; 26(2):221-225.

17 Lechtenberg R, Worner TM. Total ethanol consumption as a seizure risk factor in alcoholics. *Acta Neurologica Scandinavica.* 1992; 85(2):90-94.

18 Palmstierna T. A model for predicting alcohol withdrawal delirium. *Psychiatric Services.* 2001; 52(6):820-823.

19 Ferguson JA, Suelzer CJ, Eckert GJ et al. Risk factors for delirium tremens development. *Journal of General Internal Medicine.* 1996; 11(7):410-414.

20 Kraemer KL, Mayo SM, Calkins DR. Independent clinical correlates of severe alcohol withdrawal. *Substance Abuse.* 2003; 24(4):197-209.

21 Malcolm R, Roberts JS, Wang W et al. Multiple previous detoxifications are associated with less responsive treatment and heavier drinking during an index outpatient detoxification. *Alcohol.* 2000; 22(3):159-164.

22 Kraemer KL, Mayo SM, Calkins DR. Impact of age on the severity, course, and complications of alcohol withdrawal. *Archives of Internal Medicine.* 1997; 157(19):2234-2241.

23 Vinson DC, Menezes M. Admission alcohol level: a predictor of the course of alcohol withdrawal. *Journal of Family Practice.* 1991; 33(2):161-167.

24 Parrott S, Godfrey C, Heather N et al. Cost and outcome analysis of two detoxification services. *Alcohol & Alcoholism.* 2006; 41(1):84-91.

25 Anon. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy.* 1990; 16(3):199-208.

26 Ntais C, Pakos E, Kyzas P et al. Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Reviews.* 2005;CD005063.

27 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 55 ed. London: UK: BMJ Group and RPS Publishing; 2008.

28 Datapharm Communications Limited. *electronic Medicines Compendium*. 2009. Leatherhead: UK, Datapharm Communications Limited. http://emc.medicines.org.uk/

29 Sullivan JT, Sykora K, Schneiderman J et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction.* 1989; 84(11):1353-1357.

30 Daeppen JB, Gache P, Landry U et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Archives of Internal Medicine.* 2002; 162(10):1117-1121.

31 Saitz R, Mayo-Smith MF, Roberts MS et al. Individualized treatment for alcohol withdrawal: A randomized double- blind controlled trial. *Journal of the American Medical Association.* 1994; 272(7):519-523.

32 Weaver MF, Hoffman HJ, Johnson RE et al. Alcohol withdrawal pharmacotherapy for inpatients with medical comorbidity. *Journal of Addictive Diseases.* 2006; 25(2):17-24.

33 Lange-Asschenfeldt C, Muller MJ, Szegedi A et al. Symptom-triggered versus standard chlormethiazole treatment of inpatient alcohol withdrawal: clinical implications from a chart analysis. *European Addiction Research.* 2003; 9(1):1-7.

34 Jaeger TM, Lohr RH, Shane P. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. *Mayo Clinic Proceedings.* 2001; 76(7):695-701.

35 Reoux JP, Miller K. Routine hospital alcohol detoxification practice compared to symptom triggered management with an Objective Withdrawal Scale (CIWA-Ar). *American Journal on Addictions.* 2000; 9(2):135-144.

36 Day EJ, Patel J, Georgiou G. Evaluation of a sympton-triggered front-loading detoxification technique for alcohol dependence: a pilot study. *Psychiatric Bulletin.* 2004; 28(11):407-410.

37 Jauhar P. Is daily single dosage of diazepam as effective as chlordiazepoxide in divided doses in alcohol withdrawal - A pilot study. *Alcohol & Alcoholism.* 2000; 35(2):212-214.

38 Wasilewski D, Matsumoto H, Kur E et al. Assessment of diazepam loading dose therapy of delirium tremens. *Alcohol & Alcoholism.* 1996; 31(3):273-278.

39 Manikant S, Tripathi BM, Chavan BS. Loading dose diazepam therapy for alcohol withdrawal state. *Indian Journal of Medical Research.* 1993; 98:170-173.

40 Spies CD, Otter HE, Huske B et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. *Intensive Care Medicine.* 2003; 29(12):2230-2238.

41 Sullivan JT, Swift RM, Lewis DC. Benzodiazepine requirements during alcohol withdrawal syndrome: clinical implications of using a standardized withdrawal scale. *Journal of Clinical Psychopharmacology.* 1991; 11(5):291-295.

42 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics.* 2002; 21(2):271-292.

43 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 56 ed. London: UK: BMJ Group and RPS Publishing; 2008.

44 Hillbom M, Pieninkeroinen I, Leone M. Seizures in Alcohol-Dependent Patients: Epidemiology, Pathophysiology and Management. *CNS Drugs.* 2003; 17(14):1013-1030.

45 D'Onofrio G, Rathlev NK, Ulrich AS et al. Lorazepam for the prevention of recurrent seizures related to alcohol. *New England Journal of Medicine.* 1999; 340(12):915-919.

46 Alldredge BK, Lowenstein DH, Simon RP. Placebo-controlled trial of intravenous diphenylhydantoin for short-term treatment of alcohol withdrawal seizures. *American Journal of Medicine.* 1989; 87(6):645-648.

47 Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Annals of Emergency Medicine.* 1991; 20(5):520-522.

48 Rathlev NK, D'Onofrio G, Fish SS et al. The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Annals of Emergency Medicine.* 1994; 23(3):513-518.

49 Foy A, McKay S, Ling S et al. Clinical use of a shortened alcohol withdrawal scale in a general hospital. *Internal Medicine Journal.* 2006; 36(3):150-154.

50 Foy A, March S, Drinkwater V. Use of an objective clinical scale in the assessment and management of alcohol withdrawal in a large general hospital. *Alcoholism: Clinical & Experimental Research.* 1988; 12(3):360-364.

51 Foy A, Kay J, Taylor A. The course of alcohol withdrawal in a general hospital. *QJM.* 1997; 90(4):253-261.

52 Repper-DeLisi J, Stern TA, Mitchell M et al. Successful implementation of an alcohol-withdrawal pathway in a general hospital. *Psychosomatics.* 2008; 49(4):292-299.

53 Stanley KM, Worrall CL, Lunsford SL et al. Efficacy of a symptom-triggered practice guideline for managing alcohol withdrawal syndrome in an academic medical center. *Journal of Addictions Nursing.* 2007; 18(4):207-216.

54 Pletcher MJ, Fernandez A, May TA et al. Unintended consequences of a quality improvement program designed to improve treatment of alcohol withdrawal in hospitalized patients. *Joint Commission Journal on Quality & Patient Safety.* 2005; 31(3):148-157.

55 Morgan T, Kofoed L, Petersen DB. Clinical pathway effects on treatment of the alcohol withdrawal syndrome. *South Dakota Journal of Medicine.* 1996; 49(6):195-200.

56 Hecksel KA, Bostwick JM, Jaeger TM et al. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clinic Proceedings.* 2008; 83(3):274-279.

57 DeCarolis DD, Rice KL, Ho L et al. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. *Pharmacotherapy.* 2007; 27(4):510-518.

58 Wetterling T, Weber B, Depfenhart M et al. Development of a rating scale to predict the severity of alcohol withdrawal syndrome. *Alcohol & Alcoholism.* 2006; 41(6):611-615.

59 Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics. A neuropathological study with clinical correlations. *Journal of the Neurological Sciences.* 1982; 56(2-3):233-248.

60 Blansjaar BA, Vielvoye GJ, Van Dijk JG et al. Similar brain lesions in alcoholics and Korsakoff patients: MRI, psychometric and clinical findings. *Clinical Neurology & Neurosurgery.* 1992; 94(3):197-203.

61 Harper CG. Wernicke's encephalopathy: a more common disease than realised. A neuropathological study of 51 cases. *Journal of Neurology, Neurosurgery & Psychiatry.* 1979; 42(3):226-231.

62 Harper CG, Giles M, Finlay JR. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. *Journal of Neurology, Neurosurgery & Psychiatry.* 1986; 49(4):341-345.

63 Cook CC, Hallwood PM, Thomson AD. B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. [Review] [127 refs]. *Alcohol & Alcoholism.* 1998; 33(4):317-336.

64 Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol & Alcoholism-supplement.* 2000; 35(1):2-7.

65 Chick J. Psychiatric disorders associated with alcohol misuse. *Hospital Pharmacist.* 2000; 7:251-254.

66 Wood B, Currie J, Breen K. Wernicke's encephalopathy in a metropolitan hospital. A prospective study of incidence, characteristics and outcome. *Medical Journal of Australia.* 1986; 144(1):12-16.

67 Wood B, Currie J. Presentation of acute Wernicke's encephalopathy and treatment with thiamine. *Metabolic Brain Disease.* 1995; 10(1):57-72.

68 Ambrose.M.L., Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. *Alcoholism: Clinical & Experimental Research.* 2001; 25(1):112-116.

69 Brown LM, Rowe AE, RYLE PR et al. Efficacy of Vitamin Supplementation in Chronic Alcoholics undergoing Detoxification. *Alcohol & Alcoholism.* 1983; 18(2):157-166.

70 Baines M, Bligh JG, Madden JS. Tissue thiamin levels of hospitalised alcoholics before and after oral or parenteral vitamins. *Alcohol & Alcoholism.* 1988; 23(1):49-52.

71 Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations*. Philadelphia: F A Davis; 1971.

72 Bingel A. Uber die Parenchympunktion der Leber. *Verhandlungen der Deutschen Gesellschaft fur Innere Medizin.* 1923; 35:210-212.

73 Elphick DA, Dube AK, McFarlane E et al. Spectrum of liver histology in presumed decompensated alcoholic liver disease. *American Journal of Gastroenterology.* 2007; 102(4):780-788.

74 Thabut D, Naveau S, Charlotte F et al. The diagnostic value of biomarkers (AshTest) for the prediction of alcoholic steato-hepatitis in patients with chronic alcoholic liver disease. *Journal of Hepatology.* 2006; 44(6):1175-1185.

75 Vanbiervliet G, Le Breton F, Rosenthal-Allieri MA et al. Serum C-reactive protein: A non-invasive marker of alcoholic hepatitis. *Scandinavian Journal of Gastroenterology.* 2006; 41(12):1473-1479.

76 Kryger P, Schlichting P, Dietrichson O et al. The accuracy of the clinical diagnosis in acute hepatitis and alcoholic liver disease. Clinical versus morphological diagnosis. *Scandinavian Journal of Gastroenterology.* 1983; 18(5):691-696.

77 Talley NJ, Roth A, Woods J et al. Diagnostic value of liver biopsy in alcoholic liver disease. *Journal of Clinical Gastroenterology.* 1988; 10(6):647-650.

78 van Ness M, Diehl AM. Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? *Annals of Internal Medicine.* 1989; 111(6):473-478.

79 Goldberg S, Mendenhall C, Anderson S. VA cooperative study on alcoholic hepatitis. IV. The significance of clinically mild alcoholic hepatitis - Describing the population with minimal hyperbilirubinemia. *American Journal of Gastroenterology.* 1986; 81(11):1029-1034.

80 Ireland A, Hartley L, Ryley N et al. Raised gamma-glutamyltransferase activity and the need for liver biopsy. *British Medical Journal.* 1991; 302(6773):388-389.

81 Kitadai M, Itoshima T, Hattori S et al. Comparative diagnosis of alcoholic liver diseases by multivariate and histological analysis. *Acta Medica Okayama.* 1985; 39(1):11-18.

82 Myers RP, Fong A, Shaheen AAM. Utilization rates, complications and costs of percutaneous liver biopsy: A population-based study including 4275 biopsies. *Liver International.* 2008; 28(5):705-712.

83 Piccinino F, Sagnelli E, Pasquale G et al. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *Journal of Hepatology.* 1986; 2(2):165-173.

84 McGill DB, Rakela J, Zinsmeister AR et al. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology.* 1990; 99(5):1396-1400.

85 Maharaj B, Bhoora IG. Complications associated with percutaneous needle biopsy of the liver when one, two or three specimens are taken. *Postgraduate Medical Journal.* 1992; 68(806):964-967.

86 Colombo M, Del NE, de FR et al. Ultrasound-assisted percutaneous liver biopsy: superiority of the Tru-Cut over the Menghini needle for diagnosis of cirrhosis. *Gastroenterology.* 1988; 95(2):487-489.

87 Gilmore IT, Burroughs A, Murray LI et al. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut.* 1995; 36(3):437-441.

88 van der Poorten D, Kwok A, Lam T et al. Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. *Internal Medicine Journal.* 2006; 36(11):692-699.

89 Firpi RJ, Soldevila PC, Abdelmalek MF et al. Short recovery time after percutaneous liver biopsy: should we change our current practices? *Clinical Gastroenterology & Hepatology.* 2005; 3(9):926-929.

90 Manolakopoulos S, Triantos C, Bethanis S et al. Ultrasound-guided liver biopsy in real life: comparison of same-day prebiopsy versus real-time ultrasound approach. *Journal of Gastroenterology & Hepatology.* 2007; 22(9):1490-1493.

91 Wawrzynowicz SM, Kruszewski T, Boron KA. Complications of percutaneous liver biopsy. *Romanian Journal of Gastroenterology.* 2002; 11(2):105-107.

92 Douds AC, Joseph AE, Finlayson C et al. Is day case liver biopsy underutilised? *Gut.* 1995; 37(4):574-575.

93 Perrault J, McGill DB, Ott BJ et al. Liver biopsy: complications in 1000 inpatients and outpatients. *Gastroenterology.* 1978; 74(1):103-106.

94 Gamble P, Colapinto RF, Stronell RD. Transjugular liver biopsy: A review of 461 biopsies. *Radiology.* 1985; 157(3):589-593.

95 Velt PM, Choy OG, Shimkin PM et al. Transjugular liver biopsy in high-risk patients with hepatic disease. *Radiology.* 1984; 153(1):91-93.

96 Vlavianos P, Bird G, Portmann B et al. Transjugular liver biopsy: Use in a selected high risk population. *European Journal of Gastroenterology & Hepatology.* 1991; 3(6):469-472.

97 Department of Health. *NHS reference costs 2006-07*. 2009. UK, Department of Health. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571

98 Ratziu V, Charlotte F, Heurtier A et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology.* 2005; 128(7):1898-1906.

99 Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *Journal of Hepatology.* 2001; 35(2):195-199.

100 Neuberger J, Schulz KH, Day C et al. Transplantation for alcoholic liver disease. *Journal of Hepatology.* 2002; 36(1):130-137.

101 Neuberger J, Gimson A, Davies M et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. *Gut.* 2008; 57(2):252-257.

102 Veldt BJ, Laine F, Guillygomarc'h A et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *Journal of Hepatology.* 2002; 36(1):93-98.

103 Longworth L, Young T, Buxton MJ et al. Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. *Liver Transplantation.* 2003; 9:1295-1307.

104 Maddrey WC, Boitnott JK, Bedine MS et al. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology.* 1978; 75(2):193-199.

105 Helman RA, Temko MH, Nye SW et al. Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. *Annals of Internal Medicine.* 1971; 74(3):311-321.

106 Porter HP, Simon FR, Pope CE et al. Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. *New England Journal of Medicine.* 1971; 284(24):1350-1355.

107 Campra JL, Hamlin EM, Jr., Kirshbaum RJ et al. Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. *Annals of Internal Medicine.* 1973; 79(5):625-631.

108 Blitzer BL, Mutchnick MG, Joshi PH et al. Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. *American Journal of Digestive Diseases.* 1977; 22(6):477-484.

109 Shumaker JB, Resnick RH, Galambos JT et al. A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. *American Journal of Gastroenterology.* 1978; 69(4):443-449.

110 Lesesne HR, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. *Gastroenterology.* 1978; 74(2:Pt 1):t-73.

111 Depew W, Boyer T, Omata M et al. Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. *Gastroenterology.* 1980; 78(3):524-529.

112 Mendenhall CL, Anderson S, Garcia PP et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *New England Journal of Medicine.* 1984; 311(23):1464-1470.

113 Carithers RL, Jr., Herlong HF, Diehl AM et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. *Annals of Internal Medicine.* 1989; 110(9):685-690.

114 Ramond MJ, Poynard T, Rueff B et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *New England Journal of Medicine.* 1992; 326(8):507-512.

115 Theodossi A, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut.* 1982; 23(1):75-79.

116 Mathurin P, Mendenhall CL, Carithers RL, Jr. et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *Journal of Hepatology.* 2002; 36(4):480-487.

117 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 57 ed. London:UK: BMJ Group and RPS Publishing; 2009.

118 Nasrallah SM, Galambos JT. Aminoacid therapy of alcoholic hepatitis. *Lancet.* 1980; 2(8207):1276-1277.

119 Diehl AM, Goodman Z, Ishak KG. Alcohollike liver disease in nonalcoholics. A clinical and histologic comparison with alcohol-induced liver injury. *Gastroenterology.* 1988; 95(4):1056-1062.

120 Cabre E, Rodriguez IP, Caballeria J et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. *Hepatology.* 2000; 32(1):36-42.

121 Kearns PJ, Young H, Garcia G et al. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology.* 1992; 102(1):200-205.

122 Cabre E, Gonzalez HF, Abad LA et al. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial. *Gastroenterology.* 1990; 98(3):715-720.

123 Mendenhall CL, Bongiovanni G, Goldberg S et al. VA Cooperative Study on Alcoholic Hepatitis. III: Changes in protein-calorie malnutrition associated with 30 days of hospitalization with and without enteral nutritional therapy. *Journal of Parenteral & Enteral Nutrition.* 1985; 9(5):590-596.

124 Gupta R, Patel K, Calder PC et al. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis (APACHE II > or =6). *Pancreatology.* 2003; 3(5):406-413.

125 Buscail L, Escourrou J, Moreau J et al. Endoscopic ultrasonography in chronic pancreatitis: a comparative prospective study with conventional ultrasonography, computed tomography, and ERCP. *Pancreas.* 1995; 10(3):251-257.

126 Swobodnik W, Meyer W, Brecht K. Ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the morphologic diagnosis of pancreatic disease. *Klinische Wochenschrift.* 1983; 61(6):291-296.

127 Rosch T, Schusdziarra V, Born P et al. Modern imaging methods versus clinical assessment in the evaluation of hospital in-patients with suspected pancreatic disease. *American Journal of Gastroenterology.* 2000; 95(9):2261-2270.

128 Anon. UK guidelines for the management of acute pancreatitis. *Gut.* 2005; 54(Suppl 3):iii1-iii9.

129 Basinski A, Stefaniak T, Vingerhoets A et al. Effect of NCPB and VSPL on pain and quality of life in chronic pancreatitis patients. *World Journal of Gastroenterology.* 2005; 11(32):5010-5014.

130 Cahen DL, Gouma DJ, Nio Y et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *New England Journal of Medicine.* 2007; 356(7):676-684.

131 Dite P, Ruzicka M, Zboril V et al. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy.* 2003; 35(7):553-558.

132 Lankisch PG, Lohr HA, Otto J et al. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. *Digestion.* 1993; 54(3):148-155.

133 Nealon WH, Townsend CM, Jr., Thompson JC. Operative drainage of the pancreatic duct delays functional impairment in patients with chronic pancreatitis. A prospective analysis. *Annals of Surgery.* 1988; 208(3):321-329.

134 Alexakis N, Connor S, Ghaneh P et al. Influence of opioid use on surgical and long-term outcome after resection for chronic pancreatitis. *Surgery.* 2004; 136(3):600-608.

135 Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? *British Medical Journal.* 2000; 320(7243):1197-1200.

136 Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. *Annals of Surgery.* 1976; 183(6):667-671.

137 Craig RM, Dordal E, Myles L. Letter: The use of ampicillin in acute pancreatitis. *Annals of Internal Medicine.* 1975; 83(6):831-832.

138 Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. *Journal of Surgical Research.* 1975; 18(2):197-200.

139 Dellinger EP, Tellado JM, Soto NE et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Annals of Surgery.* 2007; 245(5):674-683.

140 Garcia-Barrasa A, Borobia FG, Pallares R et al. A Double-blind, Placebo-controlled Trial of Ciprofloxacin Prophylaxis in Patients with Acute Necrotizing Pancreatitis. *Journal of Gastrointestinal Surgery.* 2008;

141 Isenmann R, Runzi M, Kron M et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology.* 2004; 126(4):997-1004.

142 Pederzoli P, Bassi C, Vesentini S et al. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surgery, Gynecology & Obstetrics.* 1993; 176(5):480-483.

143 Sainio V, Kemppainen E, Puolakkainen P et al. Early antibiotic treatment in acute necrotising pancreatitis. *Lancet.* 1995; 346(8976):663-667.

144 Schwarz M, Isenmann R, Meyer H et al. Antibiotic use in necrotizing pancreatitis. Results of a controlled study (English Abstract). *Deutsche Medizinische Wochenschrift.* 1997; 122(12):356-361.

145 Nordback I, Sand J, Saaristo R et al. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis--a single-center randomized study. *Journal of Gastrointestinal Surgery.* 2001; 5(2):113-118.

146 Windsor AC, Kanwar S, Li AG et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut.* 1998; 42(3):431-435.

147 Olaah A, Pardavi G, Belaagyi T et al. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition.* 2002; 18(3):259-262.

148 Eckerwall GE, Tingstedt BB, Bergenzaun PE et al. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery--a randomized clinical study. *Clinical Nutrition.* 2007; 26(6):758-763.

149 Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Digestive Surgery.* 2006; 23(5-6):336-344.

150 Eckerwall GE, Axelsson JB, Andersson RG. Early nasogastric feeding in predicted severe acute pancreatitis: A clinical, randomized study. *Annals of Surgery.* 2006; 244(6):959-965.

151 Kumar A, Singh N, Prakash S et al. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *Journal of Clinical Gastroenterology.* 2006; 40(5):431-434.

152 Eatock FC, Chong P, Menezes N et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *American Journal of Gastroenterology.* 2005; 100(2):432-439.

153 Kalfarentzos F, Kehagias J, Mead N et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *British Journal of Surgery.* 1997; 84(12):1665-1669.

154 McClave SA, Greene LM, Snider HL et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *Journal of Parenteral & Enteral Nutrition.* 1997; 21(1):14-20.

155 Sax HC, Warner BW, Talamini MA et al. Early total parenteral nutrition in acute pancreatitis: lack of beneficial effects. *American Journal of Surgery.* 1987; 153(1):117-124.

156 Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *American Journal of Gastroenterology.* 2002; 97(9):2255-2262.

157 Xian-li H, Qing-jiu M, Jian-guo L et al. Effect of total parenteral nutrition (TPN) with and without glutamine dipeptide supplementation on outcome in severe acute pancreatitis (SAP). *Clinical Nutrition Supplements.* 2004; 1(1):43-47.

158 Petrov MS, Pylypchuk RD, Emelyanov NV. Systematic review: Nutritional support in acute pancreatitis. *Alimentary Pharmacology & Therapeutics.* 2008; 28(6):704-712.

159 Petrov MS, Correia MITD, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. *Journal of the Pancreas.* 2008; 9(4):440-448.

160 Eckerwall G, Olin H, Andersson B et al. Fluid resuscitation and nutritional support during severe acute pancreatitis in the past: what have we learned and how can we do better? *Clinical Nutrition.* 2006; 25(3):497-504.

161 Louie BE, Noseworthy T, Hailey D et al. 2004 MacLean-Mueller prize enteral or parenteral nutrition for severe pancreatitis: a randomized controlled trial and health technology assessment. *Canadian Journal of Surgery.* 2005; 48(4):298-306.

162 Isaksson G, Ihse I. Pain reduction by an oral pancreatic enzyme preparation in chronic pancreatitis. *Digestive Diseases & Sciences.* 1983; 28(2):97-102.

163 Slaff J, Jacobson D, Tillman CR. Protease-specific suppression of pancreatic exocrine secretion. *Gastroenterology.* 1984; 87(1):44-52.

164 Halgreen H, Thorsgaard P, Worning H. Symptomatic effect of pancreatic enzyme therapy in patients with chronic pancreatitis. *Scandinavian Journal of Gastroenterology.* 1986; 21(1):104-108.

165 Lankisch PG, Lembcke B. Therapy of pancreatogenic steatorrhoea: does acid protection of pancreatic enzymes offer any advantage? *Zeitschrift für Gastroenterologie.* 1986; 24(12):753-757.

166 Ramo OJ, Puolakkainen PA, Seppala K et al. Self-administration of enzyme substitution in the treatment of exocrine pancreatic insufficiency. *Scandinavian Journal of Gastroenterology.* 1989; 24(6):688-692.

167 Gouerou H. Alipase versus nonenteric-coated enzymes in pancreatic insufficiency. A french multicenter crossover comparative study. *International Journal of Pancreatology.* 1989; 5 Suppl:45-50.

168 Delchier JC, Vidon N, Saint MGM et al. Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two pancreatic enzyme preparations. *Alimentary Pharmacology & Therapeutics.* 1991; 5(4):365-378.

169 Mossner J, Secknus J, Meyer J et al. Treatment of pain with pancreatic extracts in chronic pancreatitis: Results of a prospective placebo-controlled multicenter trial. *Digestion.* 1992; 53(1-2):54-2.

170 Delhaye M. Comparative evaluation of a high lipase pancreatic enzyme preparation and a standard pancreatic supplement for treating exocrine pancreatic insufficiency in chronic pancreatitis. *European Journal of Gastroenterology & Hepatology.* 1996; 8(7):699-703.

171 Van Hoozen CM, Peeke PG, Taubeneck M et al. Efficacy of enzyme supplementation after surgery for chronic pancreatitis. *Pancreas.* 1997; 14(2):174-180.

172 O'Keefe SJ, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. *Journal of Clinical Gastroenterology.* 2001; 32(4):319-323.

173 Vecht J. Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. *Journal of Clinical Gastroenterology.* 2006; 40(8):721-725.

174 Dutta SK, Tilley DK. The pH-sensitive enteric-coated pancreatic enzyme preparations: an evaluation of therapeutic efficacy in adult patients with pancreatic insufficiency. *Journal of Clinical Gastroenterology.* 1983; 5(1):51-54.

175 Schneider MU, Knoll RM, Domschke S et al. Pancreatic enzyme replacement therapy: comparative effects of conventional and enteric-coated microspheric pancreatin and acid-stable fungal enzyme preparations on steatorrhoea in chronic pancreatitis. *Hepato-Gastroenterology.* 1985; 32(2):97-102.

176 Mossner J. Is there a place for pancreatic enzymes in the treatment of pain in chronic pancreatitis? *Digestion.* 1993; 54(suppl 2):35-39.

177 Pharmaceutical Press. *Martindale: the complete drug reference*. London: UK: Pharmaceutical Press; 2008.

178 Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2008.* Canterbury: UK: Personal Social Services Research Unit, 2008.

179 Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford University Press; 2006.

180 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Evaluation of Health Care Programmes*. 3 ed. Oxford University Press; 2005.

181 Kowalczyk LM, Draganov PV. Endoscopic therapy for chronic pancreatitis: technical success, clinical outcomes, and complications. *Current Gastroenterology Reports.* 2009; 11(2):111-118.

182 Cremer M, Deviere J, Delhaye M et al. Stenting in severe chronic pancreatitis: results of medium-term follow-up in seventy-six patients. *Endoscopy.* 1991; 23(3):171-176.

183 Smits ME, Badiga SM, Rauws EA et al. Long-term results of pancreatic stents in chronic pancreatitis. *Gastrointestinal Endoscopy.* 1995; 42(5):461-467.

184 Cahen D, Rauws E, Fockens P et al. Endoscopic drainage of pancreatic pseudocysts: long-term outcome and procedural factors associated with safe and successful treatment. *Endoscopy.* 2005; 37(10):977-983.

185 Smits ME, Rauws EA, van Gulik TM et al. Long-term results of endoscopic stenting and surgical drainage for biliary stricture due to chronic pancreatitis. *British Journal of Surgery.* 1996; 83(6):764-768.

186 Deviere J, Devaere S, Baize M et al. Endoscopic biliary drainage in chronic pancreatitis. *Gastrointestinal Endoscopy.* 1990; 36(2):96-100.

187 Deviere J, Cremer M, Baize M et al. Management of common bile duct stricture caused by chronic pancreatitis with metal mesh self expandable stents. *Gut.* 1994; 35(1):122-126.

188 Barthet M, Bernard JP, Duval JL et al. Biliary stenting in benign biliary stenosis complicating chronic calcifying pancreatitis. *Endoscopy.* 1994; 26(7):569-572.

189 Cahen DL, van Berkel AM, Oskam D et al. Long-term results of endoscopic drainage of common bile duct strictures in chronic pancreatitis. *European Journal of Gastroenterology & Hepatology.* 2005; 17(1):103-108.

190 Sielezneff I, Malouf A, Salle E et al. Long term results of lateral pancreaticojejunostomy for chronic alcoholic pancreatitis. *European Journal of Surgery.* 2000; 166(1):58-64.

191 Adams DB, Ford MC, Anderson MC. Outcome after lateral pancreaticojejunostomy for chronic pancreatitis. *Annals of Surgery.* 1994; 219(5):481-487.

192 Lucas CE, McIntosh B, Paley D et al. Surgical decompression of ductal obstruction in patients with chronic pancreatitis. *Surgery.* 1999; 126(4):790-797.

193 Rosch T, Daniel S, Scholz M et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. *Endoscopy.* 2002; 34(10):765-771.

194 Binmoeller KF, Jue P, Seifert H et al. Endoscopic pancreatic stent drainage in chronic pancreatitis and a dominant stricture: long-term results. *Endoscopy.* 1995; 27(9):638-644.

195 Bornman PC, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Chronic pancreatitis. *British Medical Journal.* 2001; 322(7287):660-663.

196 Office for National Statistics. *Life Expectancy: life expectancy continues to rise*. 2008. Ofice for National Statistics. http://www.statistics.gov.uk/cci/nugget.asp?ID=168

197 Schnelldorfer T, Adams DB. Surgical treatment of alcohol-associated chronic pancreatitis: The challenges and pitfalls. *American Surgeon.* 2008; 74(6):503-507.

198 Schnelldorfer T, Adams DB. Outcome after lateral pancreaticojejunostomy in patients with chronic pancreatitis associated with pancreas divisum. *American Surgeon.* 2003; 69(12):1041-1044.

199 Kalady MF, Broome AH, Meyers WC et al. Immediate and long-term outcomes after lateral pancreaticojejunostomy for chronic pancreatitis. *American Surgeon.* 2001; 67(5):478-483.

200 Terrace JD, Paterson HM, Garden OJ et al. Results of decompression surgery for pain in chronic pancreatitis. *HPB.* 2007; 9(4):308-311.

201 Madura JA, Canal DF, Lehman GA et al. Wall stent-enhanced lateral pancreaticojejunostomy for small-duct pancreatitis. *Archives of Surgery.* 2003; 138(6):644-650.

202 Rios GA, Adams DB, Yeoh KG et al. Outcome of lateral pancreaticojejunostomy in the management of chronic pancreatitis with nondilated pancreatic ducts. *Journal of Gastrointestinal Surgery.* 1998; 2(3):223-229.