DRUG MISUSE: OPIOID DETOXIFICATION

THE NICE GUIDELINE

NATIONAL
COLLABORATING
CENTRE FOR
MENTAL HEALTH

DRUG MISUSE

Opioid detoxification

National Clinical Practice Guideline Number 52

National Collaborating Centre for Mental Health
commissioned by the
National Institute for Health & Clinical Excellence

published by
The British Psychological Society and The Royal College of Psychiatrists

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

ISBN-: 978-1-85433-469-5

Printed in Great Britain by Alden Press.

Additional material: data CD-ROM created by Pixl8 (www.pixl8.co.uk)

developed by National Collaborating Centre for Mental Health
Royal College of Psychiatrists' Research and Training Unit
4th Floor, Standon House
21 Mansell Street
London
E1 8AA
www.nccmh.org.uk

commissioned by National Institute for Health and Clinical Excellence
MidCity Place, 71 High Holborn
London
WCIV 6NA
www.nice.org.uk

published by The British Psychological Society
St Andrews House
48 Princess Road East
Leicester
LE1 7DR
www.bps.org.uk

and

The Royal College of Psychiatrists
17 Belgrave Square
London
SW1X 8PG
www.rcpsych.ac.uk

The British Psychological Society

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GUIDELINE DEVELOPMENT GROUP MEMBERS

Dr Clare Gerada (Chair, Guideline Development Group)
General Practitioner, Lambeth Primary Care Trust, London
Primary Care Lead for Drug Misuse at the Royal College of General Practitioners

Mr Stephen Pilling (Facilitator, Guideline Development Group)
Joint Director, The National Collaborating Centre for Mental Health
Director, Centre for Outcomes, Research and Effectiveness, University College London
Consultant Clinical Psychologist and Deputy Head of Psychology Services, Camden and Islington Mental Health and Social Care Trust

Mrs Pauline Bissett
Chief Executive, Broadway Lodge

Mr Neil Connelly
Service User Representative, Voluntary Support Worker, Littledale Hall Therapeutic Community, Lancaster

Dr Paul Davis
Consultant Lead Clinical Psychologist and Head of Psychology for Substance Misuse Services, Camden and Islington Mental Health and Social Care Trust

Ms Vivienne Evans
Carer Representative
Chief Executive, Adfam

Dr Emily Finch
Addiction Psychiatrist, South London and Maudsley NHS Foundation Trust
Clinical Team Lead, National Treatment Agency for Substance Misuse

Professor Robert Forrest
Consultant in Clinical Chemistry and Toxicology, Sheffield Teaching Hospitals NHS Foundation Trust

Dr Eilish Gilvarry
Clinical Director, Newcastle Drug and Alcohol Unit, Newcastle upon Tyne

Mr David Harding-Price
Team Coordinator, Community Mental Health Team, Skegness, Lincolnshire

Mr Paul Hawkins
Service User Representative

Ms Sarah Hopkins
Project Manager, The National Collaborating Centre for Mental Health (2006–2007)

Guideline development group members

Ms Rebecca King
Project Manager, The National Collaborating Centre for Mental Health (2005–2006)

Mr Ryan Li
Research Assistant, The National Collaborating Centre for Mental Health

Dr Anne Lingford-Hughes
Reader in Biological Psychiatry and Addiction, Academic Unit of Psychiatry, University of Bristol
Addiction Psychiatrist, Avon and Wiltshire Mental Health Partnership NHS Trust

Dr Nicholas Meader
Systematic Reviewer, The National Collaborating Centre for Mental Health

Ms Jan Palmer
Nurse Consultant, Clinical Substance Misuse Lead, Offender Health

Mrs Kay Roberts
Pharmacist; Chairman, PharMAG

Ms Poonam Sood
Research Assistant, The National Collaborating Centre for Mental Health

Ms Sarah Stockton
Information Scientist, The National Collaborating Centre for Mental Health

Dr Clare Taylor
Editor, The National Collaborating Centre for Mental Health

Mr Loukas Xaplanteris
Health Economist, The National Collaborating Centre for Mental Health

ACKNOWLEDGEMENTS

The Guideline Development Group for Drug Misuse: Opioid Detoxification and the National Collaborating Centre for Mental Health (NCCMH) review team would like to thank the following people:

Those who acted as advisors on specialist topics or have contributed to the process by meeting with the Guideline Development Group:

Dr Ed Day, University of Birmingham
Professor Michael Gossop, Institute of Psychiatry
Dr Kim Wolff, Institute of Psychiatry

Editorial assistance
Emma Brown

1. EXECUTIVE SUMMARY

KEY PRIORITIES FOR IMPLEMENTATION

The following recommendations have been identified as recommendations for implementation.

Providing information, advice and support

- Detoxification should be a readily available treatment option for people who are opioid dependent and have expressed an informed choice to become abstinent. *See section 3.7.*
- In order to obtain informed consent, staff should give detailed information to service users about detoxification and the associated risks, including:
  - the physical and psychological aspects of opioid withdrawal, including the duration and intensity of symptoms, and how these may be managed
  - the use of non-pharmacological approaches to manage or cope with opioid withdrawal symptoms
  - the loss of opioid tolerance following detoxification, and the ensuing increased risk of overdose and death from illicit drug use that may be potentiated by the use of alcohol or benzodiazepines
  - the importance of continued support, as well as psychosocial and appropriate pharmacological interventions, to maintain abstinence, treat comorbid mental health problems and reduce the risk of adverse outcomes (including death). *See section 3.7.*

The choice of medication for detoxification

- Methadone or buprenorphine should be offered as the first-line treatment in opioid detoxification. When deciding between these medications, healthcare professionals should take into account:
  - whether the service user is receiving maintenance treatment with methadone or buprenorphine; if so, opioid detoxification should normally be started with the same medication
  - the preference of the service user. *See section 6.3.*

Ultra-rapid detoxification

- Ultra-rapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death. *See section 6.5.8.*

The choice of setting for detoxification

- Staff should routinely offer a community-based programme to all service users considering opioid detoxification. Exceptions to this may include service users who:
  - have not benefited from previous formal community-based detoxification
  - need medical and/or nursing care because of significant comorbid physical or mental health problems
  - require complex polydrug detoxification, for example concurrent detoxification from alcohol or benzodiazepines
  - are experiencing significant social problems that will limit the benefit of community-based detoxification. *See section 8.2.3.*

1.1 GENERAL CONSIDERATIONS

1.1.1 Providing information, advice and support

1.1.1.1 Detoxification should be a readily available treatment option for people who are opioid dependent and have expressed an informed choice to become abstinent.

1.1.1.2 In order to obtain informed consent, staff should give detailed information to service users about detoxification and the associated risks, including:

- the physical and psychological aspects of opioid withdrawal, including the duration and intensity of symptoms, and how these may be managed
- the use of non-pharmacological approaches to manage or cope with opioid withdrawal symptoms
- the loss of opioid tolerance following detoxification, and the ensuing increased risk of overdose and death from illicit drug use that may be potentiated by the use of alcohol or benzodiazepines
- the importance of continued support, as well as psychosocial and appropriate pharmacological interventions, to maintain abstinence, treat comorbid mental health problems and reduce the risk of adverse outcomes (including death).

1.1.1.3 Service users should be offered advice on aspects of lifestyle that require particular attention during opioid detoxification. These include:

- a balanced diet
- adequate hydration
- sleep hygiene
- regular physical exercise.

1.1.1.4 Staff who are responsible for the delivery and monitoring of a care plan should:

- develop and agree the plan with the service user

- establish and sustain a respectful and supportive relationship with the service user
- help the service user to identify situations or states when he or she is vulnerable to drug misuse and to explore alternative coping strategies
- ensure that all service users have full access to a wide range of services
- ensure that maintaining the service user's engagement with services remains a major focus of the care plan
- review regularly the care plan of a service user receiving maintenance treatment to ascertain whether detoxification should be considered
- maintain effective collaboration with other care providers.

1.1.1.5 People who are opioid dependent and considering self-detoxification should be encouraged to seek detoxification in a structured treatment programme or, at a minimum, to maintain contact with a drug service.

1.1.1.6 Service users considering opioid detoxification should be provided with information about self-help groups (such as 12-step groups) and support groups (such as the Alliance); staff should consider facilitating engagement with such services.

1.1.1.7 Staff should discuss with people who present for detoxification whether to involve their families and carers in their assessment and treatment plans. However, staff should ensure that the service user's right to confidentiality is respected.

1.1.1.8 In order to reduce loss of contact when people who misuse drugs transfer between services, staff should ensure that there are clear and agreed plans to facilitate effective transfer.

1.1.1.9 All interventions for people who misuse drugs should be delivered by staff who are competent in delivering the intervention and who receive appropriate supervision.

1.1.1.10 People who are opioid dependent should be given the same care, respect and privacy as any other person.

1.1.2 Supporting families and carers

1.1.2.1 Staff should ask families and carers about, and discuss concerns regarding, the impact of drug misuse on themselves and other family members, including children. Staff should also:

- offer family members and carers an assessment of their personal, social and mental health needs
- provide verbal and written information and advice on the impact of drug misuse on service users, families and carers
- provide information about detoxification and the settings in which it may take place
- provide information about self-help and support groups for families and carers.

1.2 ASSESSMENT

1.2.1 Clinical assessment

1.2.1.1 People presenting for opioid detoxification should be assessed to establish the presence and severity of opioid dependence, as well as misuse of and/or dependence on other substances, including alcohol, benzodiazepines and stimulants. As part of the assessment, healthcare professionals should:

- use urinalysis to aid identification of the use of opioids and other substances; consideration may also be given to other near-patient testing methods such as oral fluid and/or breath testing
- clinically assess signs of opioid withdrawal where present (the use of formal rating scales may be considered as an adjunct to, but not a substitute for, clinical assessment)
- take a history of drug and alcohol misuse and any treatment, including previous attempts at detoxification, for these problems
- review current and previous physical and mental health problems, and any treatment for these
- consider the risks of self-harm, loss of opioid tolerance and the misuse of drugs or alcohol as a response to opioid withdrawal symptoms
- consider the person's current social and personal circumstances, including employment and financial status, living arrangements, social support and criminal activity
- consider the impact of drug misuse on family members and any dependants
- develop strategies to reduce the risk of relapse, taking into account the person's support network.

1.2.1.2 If opioid dependence or tolerance is uncertain, healthcare professionals should, in addition to near-patient testing, use confirmatory laboratory tests. This is particularly important when:

- a young person first presents for opioid detoxification
- a near-patient test result is inconsistent with clinical assessment
- complex patterns of drug misuse are suspected.

1.2.1.3 Near-patient and confirmatory testing should be conducted by appropriately trained healthcare professionals in accordance with established standard operating and safety procedures.

1.2.2 Special considerations

1.2.2.1 Opioid detoxification should not be routinely offered to people:

- with a medical condition needing urgent treatment
- in police custody, or serving a short prison sentence or a short period of remand; consideration should be given to treating opioid withdrawal symptoms with opioid agonist medication

- who have presented to an acute or emergency setting; the primary emergency problem should be addressed and opioid withdrawal symptoms treated, with referral to further drug services as appropriate.

1.2.2.2 For women who are opioid dependent during pregnancy, detoxification should only be undertaken with caution.

1.2.2.3 For people who are opioid dependent and have comorbid physical or mental health problems, these problems should be treated alongside the opioid dependence, in line with relevant NICE guidance where available.

1.2.3 People who misuse benzodiazepines or alcohol in addition to opioids

1.2.3.1 If a person presenting for opioid detoxification also misuses alcohol, healthcare professionals should consider the following.

- If the person is not alcohol dependent, attempts should be made to address their alcohol misuse, because they may increase this as a response to opioid withdrawal symptoms, or substitute alcohol for their previous opioid misuse.
- If the person is alcohol dependent, alcohol detoxification should be offered. This should be carried out before starting opioid detoxification in a community or prison setting, but may be carried out concurrently with opioid detoxification in an inpatient setting or with stabilisation in a community setting.

1.2.3.2 If a person presenting for opioid detoxification is also benzodiazepine dependent, healthcare professionals should consider benzodiazepine detoxification. When deciding whether this should be carried out concurrently with, or separately from, opioid detoxification, healthcare professionals should take into account the person's preference and the severity of dependence for both substances.

1.3 PHARMACOLOGICAL INTERVENTIONS IN OPIOID DETOXIFICATION

1.3.1 The choice of medication for detoxification

1.3.1.1 Methadone or buprenorphine should be offered as the first-line treatment in opioid detoxification. When deciding between these medications, healthcare professionals should take into account:

- whether the service user is receiving maintenance treatment with methadone or buprenorphine; if so, opioid detoxification should normally be started with the same medication

- the preference of the service user.

1.3.1.2 Lofexidine may be considered for people:

- who have made an informed and clinically appropriate decision not to use methadone or buprenorphine for detoxification
- who have made an informed and clinically appropriate decision to detoxify within a short time period
- with mild or uncertain dependence (including young people).

1.3.1.3 Clonidine should not be used routinely in opioid detoxification.

1.3.1.4 Dihydrocodeine should not be used routinely in opioid detoxification.

1.3.2 Dosage and duration of detoxification

1.3.2.1 When determining the starting dose, duration and regimen (for example, linear or stepped) of opioid detoxification, healthcare professionals, in discussion with the service user, should take into account the:

- severity of dependence (particular caution should be exercised where there is uncertainty about dependence)
- stability of the service user (including polydrug and alcohol use, and comorbid mental health problems)
- pharmacology of the chosen detoxification medication and any adjunctive medication
- setting in which detoxification is conducted.

1.3.2.2 The duration of opioid detoxification should normally be up to 4 weeks in an inpatient/residential setting and up to 12 weeks in a community setting.

1.3.3 Ultra-rapid, rapid and accelerated detoxification

1.3.3.1 Ultra-rapid and rapid detoxification using precipitated withdrawal should not be routinely offered. This is because of the complex adjunctive medication and the high level of nursing and medical supervision required.

1.3.3.2 Ultra-rapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death.

1.3.3.3 Rapid detoxification should only be considered for people who specifically request it, clearly understand the associated risks and are able to manage the adjunctive medication. In these circumstances, healthcare professionals should ensure during detoxification that:

- the service user is able to respond to verbal stimulation and maintain a patent airway
- adequate medical and nursing support is available to regularly monitor the service user's level of sedation and vital signs
- staff have the competence to support airways.

1.3.3.4 Accelerated detoxification, using opioid antagonists at lower doses to shorten detoxification, should not be routinely offered. This is because of the increased severity of withdrawal symptoms and the risks associated with the increased use of adjunctive medications.

1.3.4 Adjunctive medications

1.3.4.1 When prescribing adjunctive medications during opioid detoxification, healthcare professionals should:

- only use them when clinically indicated, such as when agitation, nausea, insomnia, pain and/or diarrhoea are present
- use the minimum effective dosage and number of drugs needed to manage symptoms
- be alert to the risks of adjunctive medications, as well as interactions between them and with the opioid agonist.

1.3.5 Monitoring of detoxification medication

1.3.5.1 Healthcare professionals should be aware that medications used in opioid detoxification are open to risks of misuse and diversion in all settings (including prisons), and should consider:

- monitoring of medication concordance
- methods of limiting the risk of diversion where necessary, including supervised consumption.

1.4 OPIOID DETOXIFICATION IN COMMUNITY, RESIDENTIAL, INPATIENT AND PRISON SETTINGS

1.4.1 The choice of setting

1.4.1.1 Staff should routinely offer a community-based programme to all service users considering opioid detoxification. Exceptions to this may include service users who:

- have not benefited from previous formal community-based detoxification
- need medical and/or nursing care because of significant comorbid physical or mental health problems
- require complex polydrug detoxification, for example concurrent detoxification from alcohol or benzodiazepines
- are experiencing significant social problems that will limit the benefit of community-based detoxification.

1.4.1.2 Residential detoxification should normally only be considered for people who have significant comorbid physical or mental health problems, or who

require concurrent detoxification from opioids and benzodiazepines or sequential detoxification from opioids and alcohol.

1.4.1.3 Residential detoxification may also be considered for people who have less severe levels of opioid dependence, for example those early in their drug-using career, or for people who would benefit significantly from a residential rehabilitation programme during and after detoxification.

1.4.1.4 Inpatient, rather than residential, detoxification should normally only be considered for people who need a high level of medical and/or nursing support because of significant and severe comorbid physical or mental health problems, or who need concurrent detoxification from alcohol or other drugs that requires a high level of medical and nursing expertise.

1.4.2 Continued treatment and support after detoxification

1.4.2.1 Following successful opioid detoxification, and irrespective of the setting in which it was delivered, all service users should be offered continued treatment, support and monitoring designed to maintain abstinence. This should normally be for a period of at least 6 months.

1.4.3 Delivering detoxification

1.4.3.1 Community detoxification should normally include:

- prior stabilisation of opioid use through pharmacological treatment
- effective coordination of care by specialist or competent primary practitioners
- the provision of psychosocial interventions, where appropriate, during the stabilisation and maintenance phases *(see section 1.5)*.

1.4.3.2 Inpatient and residential detoxification should be conducted with 24-hour medical and nursing support commensurate with the complexity of the service user's drug misuse and comorbid physical and mental health problems. Both pharmacological and psychosocial interventions should be available to support treatment of the drug misuse as well as other significant comorbid physical or mental health problems.

1.4.4 Detoxification in prison settings

1.4.4.1 People in prison should have the same treatment options for opioid detoxification as people in the community. Healthcare professionals should take into account additional considerations specific to the prison setting, including:

- practical difficulties in assessing dependence and the associated risk of opioid toxicity early in treatment

- length of sentence or remand period, and the possibility of unplanned release
- risks of self-harm, death or post-release overdose.

1.5 SPECIFIC PSYCHOSOCIAL INTERVENTIONS

1.5.1 Contingency management to support opioid detoxification

1.5.1.1 Contingency management aimed at reducing illicit drug use should be considered both during detoxification and for up to 3–6 months after completion of detoxification.

1.5.1.2 Contingency management during and after detoxification should be based on the following principles.

- The programme should offer incentives (usually vouchers that can be exchanged for goods or services of the service user's choice, or privileges such as take-home methadone doses) contingent on each presentation of a drug-negative test (for example, free from cocaine or non-prescribed opioids).
- If vouchers are used, they should have monetary values that start in the region of £2 and increase with each additional, continuous period of abstinence
- The frequency of screening should be set at three tests per week for the first 3 weeks, two tests per week for the next 3 weeks, and one per week thereafter until stability is achieved.
- Urinalysis should be the preferred method of testing but oral fluid tests may be considered as an alternative.

1.5.1.3 Staff delivering contingency management programmes should ensure that:

- the target is agreed in collaboration with the service user
- the incentives are provided in a timely and consistent manner
- the service user fully understands the relationship between the treatment goal and the incentive schedule
- the incentive is perceived to be reinforcing and supports a healthy/drug-free lifestyle.

1.5.2 Implementing contingency management

1.5.2.1 Drug services should ensure that as part of the introduction of contingency management, staff are trained and competent in appropriate near-patient testing methods and in the delivery of contingency management.

1.5.2.2 Contingency management should be introduced to drug services in the phased implementation programme led by the National Treatment Agency for Substance Misuse (NTA), in which staff training and the development

of service delivery systems are carefully evaluated. The outcome of this evaluation should be used to inform the full-scale implementation of contingency management.

1.6 RESEARCH RECOMMENDATIONS

1.6.1 Adjunctive medication during detoxification

If a person needs adjunctive medication during detoxification, in addition to their opioid agonist reducing regimen or in addition to an adjunctive alpha-2 adrenergic agonist (for example, lofexidine), what medications are associated with greater safety and fewer withdrawal symptoms?

Why this is important
A large variety of adjunctive medications are used for the management of withdrawal symptoms during detoxification, particularly when alpha-2 adrenergic agonists are used. Research is needed to guide decisions on how best to manage withdrawal symptoms with minimal risk of harm to the service user.

1.6.2 Comparing inpatient or residential and community detoxification

Is inpatient or residential detoxification associated with greater probability of abstinence, better rates of completion of treatment, lower levels of relapse and increased cost effectiveness than community detoxification?

Why this is important
There have been some studies comparing inpatient or residential detoxification with community detoxification. However, these studies are often based on small sample sizes, have considerable methodological problems and have produced inconsistent results. Inpatient or residential detoxification requires significantly more resources than community detoxification, so it is important to assess whether treatment in such settings is more clinically and cost effective. If so, it is also important to understand if there are particular subgroups that are more likely to benefit from treatment in these settings.

2. INTRODUCTION

This guideline has been developed to advise on opioid detoxification for drug misuse. The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, service users, a carer and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for people who misuse drugs while also emphasising the importance of the experience of care for people who misuse drugs and their carers (see Appendix 1 for more details on the scope of the guideline).

Although the evidence base is rapidly expanding, there are a number of major gaps, and future revisions of this guideline will incorporate new scientific evidence as it develops. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, people who misuse drugs and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

2.1 NATIONAL GUIDELINES

2.1.1 What are clinical practice guidelines?

Clinical practice guidelines are 'systematically developed statements that assist clinicians and patients in making decisions about appropriate treatment for specific conditions' (Mann, 1996). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. Where evidence is lacking, the guidelines incorporate statements and recommendations based upon the consensus statements developed by the guideline development group (GDG).

Clinical guidelines are intended to improve the process and outcomes of healthcare in a number of different ways. Clinical guidelines can:

- provide up-to-date evidence-based recommendations for the management of conditions and disorders by healthcare professionals
- be used as the basis to set standards to assess the practice of healthcare professionals
- form the basis for education and training of healthcare professionals
- assist patients and carers in making informed decisions about their treatment and care
- improve communication between healthcare professionals, patients and carers
- help identify priority areas for further research.

2.1.2 Uses and limitations of clinical guidelines

Guidelines are not a substitute for professional knowledge and clinical judgement. They can be limited in their usefulness and applicability by a number of different factors: the availability of high-quality research evidence, the quality of the methodology used in the development of the guideline, the generalisability of research findings and the uniqueness of individuals who misuse drugs.

Although the quality of research in this field is variable, the methodology used here reflects current international understanding on the appropriate practice for guideline development (AGREE: Appraisal of Guidelines for Research and Evaluation Instrument; www.agreecollaboration.org), ensuring the collection and selection of the best research evidence available, and the systematic generation of treatment recommendations applicable to the majority of service users and situations. However, there will always be some people for whom clinical guideline recommendations are not appropriate and situations in which the recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in light of the service user's circumstances, in consultation with the person who misuses drugs/or carer.

In addition to the clinical evidence, cost-effectiveness information, where available, is taken into account in the generation of statements and recommendations of the clinical guidelines. While national guidelines are concerned with clinical and cost effectiveness, issues of affordability and implementation costs are to be determined by the National Health Service (NHS).

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the person and to provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered; otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care in order to support and encourage a good therapeutic relationship is at times as important as the specific treatments offered.

2.1.3 Why develop national guidelines?

The National Institute for Health and Clinical Excellence (NICE) was established as a Special Health Authority for England and Wales in 1999, with a remit to provide a single source of authoritative and reliable guidance for patients, professionals and the public. NICE guidance aims to improve standards of care, to diminish unacceptable variations in the provision and quality of care across the NHS and to ensure that the health service is patient-centred. All guidance is developed in a transparent and collaborative manner using the best available evidence and involving all relevant stakeholders.

NICE generates guidance in a number of different ways, three of which are relevant here. First, national guidance is produced by the Technology Appraisal Committee to give robust advice about a particular treatment, intervention, procedure or other health technology. Second, NICE commissions public health intervention guidance focused on types of activity (interventions) that help to reduce people's risk of developing a disease or condition or help to promote or maintain a healthy lifestyle. Third, NICE commissions the production of national clinical practice guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE has established seven National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare.

2.1.4 The National Collaborating Centre for Mental Health

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national patient and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists' Research and Training Unit and the British Psychological Society's equivalent unit (Centre for Outcomes Research and Effectiveness).

2.1.5 From national guidelines to local protocols

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving commissioners of healthcare, primary care and specialist mental health professionals, patients and carers should undertake the translation of the implementation plan into local protocols taking into account both the recommendations set out in this guideline and the priorities set in the National Service Framework (NSF) for Mental Health and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

2.1.6 Auditing the implementation of guidelines

This guideline identifies key areas of clinical practice and service delivery for local and national audit. Although the generation of audit standards is an important and necessary step in the implementation of this guidance, a more broadly based implementation strategy will be developed. Nevertheless, it should be noted that the Healthcare Commission will monitor the extent to which Primary Care Trusts, trusts

responsible for mental health and social care and Health Authorities have implemented these guidelines.

2.2 THE NATIONAL OPIOID DETOXIFICATION FOR DRUG MISUSE GUIDELINE

2.2.1 Who has developed this guideline?

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included two service users and a carer, and professionals from psychiatry, clinical psychology, pharmacy, toxicology, nursing, general practice, the prison service, the National Treatment Agency for Substance Misuse (NTA) and the private and voluntary sectors.

Staff from the NCCMH provided leadership and support throughout the process of guideline development, undertaking systematic searches, information retrieval, appraisal and systematic review of the evidence. Members of the GDG received training in the process of guideline development from NCCMH staff and the service users and carer received training and support from the NICE Patient and Public Involvement Programme. The NICE Guidelines Technical Advisor provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of nine times throughout the process of guideline development. The GDG met as a whole, but key topics were led by a national expert in the relevant topic. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisors where needed. The group oversaw the production and synthesis of research evidence before presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

2.2.2 For whom is this guideline intended?

This guideline will be relevant for adults and young people who misuse drugs.

The guideline covers the care provided by primary, community, secondary, tertiary, and other healthcare professionals who have direct contact with, and make decisions concerning the care of adults and young people who misuse drugs.

The guideline will also be relevant to the work, but will not cover the practice, of those in:

- occupational health services
- social services
- the independent sector.

The experience of drug misuse can affect the whole family and often the community. The guideline recognises the role of both in the treatment and support of people who misuse drugs.

2.2.3 Specific aims of this guideline

The guideline makes recommendations for the opioid detoxification for drug misuse. Specifically, it aims to:

- evaluate the role of opioid detoxification in the treatment of drug misuse
- evaluate the role of specific psychosocial interventions in combination with opioid detoxification in the treatment of drug misuse
- integrate the above to provide best practice advice on the care of individuals throughout the course of their drug misuse
- promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.

2.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide a summary of the clinical practice and research recommendations, a general introduction to guidelines and an introduction to the drug misuse topic. The fourth chapter provides a summary of the methods used to develop the recommendations. Chapters 5 to 9 provide the evidence that underpins the recommendations.

Each evidence chapter begins with a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted. Therefore, the structure of the chapters varies accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about both the interventions included and the studies considered for review. Clinical summaries are then used to summarise the evidence presented. Finally, recommendations related to each topic are presented at the end of each relevant section of a chapter. On the CD-ROM, full details about the reviewed studies can be found in Appendix 15. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 16 (see Text Box 1 for details) and evidence profile tables in Appendix 17.

Text Box 1: Appendices on CD-ROM

Content	Appendix
Reviewed studies	Appendix 15
Forest plots	Appendix 16
Evidence profile tables	Appendix 17

3. INTRODUCTION TO DRUG MISUSE

3.1 DRUG MISUSE AND OPIOID DEPENDENCE

This guideline is concerned with detoxification from opioid dependence. Of the estimated 4 million people in the UK who use illicit drugs each year (cannabis being by far the most commonly used), approximately 50,000 people misuse opioids, although this may be an underestimate (Roe & Man, 2006). Opioid misuse is also associated with much greater rates of harm than misuse of either cannabis or cocaine. Over 150,000 people are in treatment for opioid misuse and are prescribed opioids such as methadone and buprenorphine (NTA, 2005a; Hay *et al.*, 2006).

The term 'opioids' refers to a class of psychoactive substances derived from the poppy plant (including opium, morphine and codeine), as well as semi-synthetic forms (including heroin) and synthetic compounds (including methadone and buprenorphine) with similar properties (WHO, 2006). Illicit use of opioids generally involves injecting, or inhaling the fumes produced by heating the drug. The term 'opiate' refers strictly to the subset of opioids that are naturally occurring or semi-synthetic, and therefore includes heroin and morphine but excludes methadone and buprenorphine.

Drug misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines (WHO, 2006). It has a negative impact on health or functioning and may take the form of drug dependence, or be part of a wider spectrum of problematic or harmful behaviour (DH, 2006). In the UK, the Advisory Council on the Misuse of Drugs (ACMD) characterises problem drug use as a condition that may cause an individual to experience social, psychological, physical or legal problems related to intoxication and/or regular excessive consumption, and/or dependence (ACMD, 1998).

In this guideline, dependence is defined as a strong desire or compulsion to take a substance, a difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others (WHO, 2006). Dependence is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) when three or more of the following criteria are present in a 12-month period: tolerance; withdrawal; increasing use over time; persistent or unsuccessful attempts to reduce use; preoccupation or excessive time spent on use or recovery from use; negative impact on social, occupational or recreational activity; and continued use despite evidence of its causing psychological or physical problems (American Psychiatric Association [APA], 1994).

The diagnosis of dependence is clearest with opioids. The WHO states that:

> *'opioid dependence develops after a period of regular use of opioids, with the time required varying according to the quantity, frequency and route of administration, as well as factors of individual vulnerability and the context in which*

> *drug use occurs. Opioid dependence is not just a heavy use of the drug but a complex health connotation that has social, psychological and biological determinants and consequences, including changes in the brain. It is not a weakness of character or will' (WHO, 2006).*

Repeated use of a drug can lead to the development of tolerance in which increased doses of the drug are required to produce the same effect. Cessation of use leads to reduced tolerance and this may present significant risks for individuals who return to drug doses at a level to which they had previously developed tolerance. This can result in accidental overdoses and, in the case of opioid misuse, respiratory depression and death.

Withdrawal syndromes have clearly been identified after cessation or reduction of opioid use. DSM-IV criteria for a withdrawal disorder include the development of a substance-specific syndrome due to cessation or reduction in use, the syndrome causing clinically significant distress, and symptoms not being due to a general medical condition or better explained by another mental disorder (APA, 1994).

Opioids also produce intoxication, that is, disturbances in psychophysiological functions and responses, including consciousness, cognition and behaviour, following administration (WHO, 2006). These are described in greater detail in Section 3.5.

People who misuse drugs may present with a range of health and social problems other than dependence, which may include (particularly with opioid users):

- physical health problems (for example, thrombosis, abscesses, overdose, hepatitis B and C, human immunodeficiency virus [HIV], and respiratory and cardiac problems)
- mental health problems (for example, depression, anxiety, paranoia and suicidal thoughts)
- social difficulties (for example, relationship problems, financial difficulties, unemployment and homelessness)
- criminal justice problems.

Many people who misuse opioids also misuse a range of other substances concurrently and regularly (known as polydrug misuse). The use of opioids alongside cocaine or crack cocaine is common, with the National Drug Treatment Monitoring System (NDTMS), which collects, collates and analyses information from those involved in the drug treatment system, reporting an increase in the use of both drugs from 18% of those presenting for drug treatment in 1998 to 24% in 2001 (NTA, 2005b). Alcohol misuse is also common in people who misuse drugs; data from the National Treatment Outcomes Research Study (NTORS) on drug misuse suggested that 22% of participants also drank alcohol frequently, 17% drank extremely heavily and 8% drank an excessive amount on a daily basis (Gossop *et al.*, 2000a). People who misuse opioids in particular may often take a cocktail of substances, including alcohol, cannabis and prescribed drugs such as benzodiazepines, which can have especially dangerous effects in comparison with one of the drugs taken individually.

Drug dependence is associated with a high incidence of criminal activity, with associated costs to the criminal justice system in the UK estimated at £1 billion per annum in 1996 (United Kingdom Anti-Drugs Coordinating Unit, 1998). For example,

more than 17,000 offences were reported by an NTORS cohort of 753 participants in a 90-day period before entering treatment (Gossop *et al.*, 2000b). Notably, most of the offences were committed by a small proportion of the cohort (10% of participants accounted for 76% of the crimes). Illicit drug use is also much more common among known offenders in the UK than among cohorts of comparable age drawn from the general population. In a sample of 1,435 arrestees drug-tested and interviewed by Bennett and colleagues (2001), 24% tested positive for opioids. The average weekly expenditure on drugs (heroin and crack/cocaine) was £290, and the main sources of illegal income were theft, burglary, robbery, handling stolen goods and fraud. The NTORS also found 61% of a drug misuse treatment sample reported committing crimes other than drug possession in the 3 months prior to starting treatment, with the most commonly reported offence being shoplifting. In addition, there is a high prevalence of drug misuse among the incarcerated population: in a 1997 survey between 41 and 54% of remand and sentenced prisoners were reported to be opioid, stimulant and/or cannabis dependent in the year prior to incarceration (Singleton *et al.*, 1999). Drug treatment can lead to significant reductions in offending levels (Gossop *et al.*, 2003) and, as a consequence, the prison and the broader criminal justice system is an increasingly significant referral source and venue for providing drug treatment.

3.2 EPIDEMIOLOGY OF DRUG MISUSE

According to the national British Crime Survey 2005/6 (Roe & Man, 2006), 34.9% of 16–59 year olds had used one or more illicit drugs in their lifetime, 10.5% in the previous year and 6.3% in the previous month. These figures are much lower for opioid use, with 0.1% of the population having used opioids (including heroin and methadone) in the previous year. However, estimates based on data that also take into account other indicators such as current service usage provide an illicit drug-use figure of 9.35 per 1,000 of the population aged 15–64 years (360,811), of whom 3.2 per 1,000 (123,498) are injecting drug users (Chivite-Matthews *et al.*, 2005). Analysis of the 2004/5 data from the NDTMS suggests that there were an estimated 160,450 people in contact with treatment services in England during that period, the majority for primary opioid misuse (NTA, 2005b). Males comprise over 70% of new presentations, and the majority of those requiring treatment are opioid dependent (typically using illicit heroin). Similar figures have emerged from Frischer and colleagues (2001), who estimated 0.5% of the population of Britain (that is, 226,000 people) to be problem drug users. More recent estimates indicate that there are around 327,000 problem drug users (of opioids and/or crack cocaine) in the UK, with 280,000 of these opioid users (Hay *et al.*, 2006).

Drug misuse is more common in certain vulnerable groups. For example, Ward and colleagues (2003) found that among care leavers aged between 14 and 24 years, drug misuse is much higher than in the general population, with three quarters of the sample having at some time misused a drug and over half having misused a drug in the previous month. Levels in the young homeless population are also much higher than the general population, with one survey finding that almost all (95%) of the

sample had at some time misused drugs, many (76%) having used cocaine, heroin, and/or amphetamine in the previous month.

3.3 AETIOLOGY AND MAINTENANCE OF DRUG MISUSE

Drug misuse is increasingly portrayed in the field as a medical disorder, known as the 'disease model' of drug misuse, in part due to advances in our understanding of the neurobiology underlying dependence (Volkow & Li, 2005). There is also no question that numerous socioeconomic and psychological factors all play an important part in the aetiology of drug misuse. These conceptualisations are not mutually exclusive; rather they are facets of the multifactorial aetiology of drug misuse.

The most robust evidence highlights peer drug use, availability of drugs and also elements of family interaction, including parental discipline and family cohesion, as significant risk factors for drug misuse (Frischer *et al.*, 2005). In particular, traumatic family experiences such as childhood neglect, homelessness or abuse increase the likelihood that the individual will develop problems with drugs later on in life (Kumpfer & Bluth, 2004). Recent studies of twins, families and people who have been adopted suggest that vulnerability to drug misuse may also have a genetic component (Prescott *et al.*, 2006), although it is unclear whether repeated use is primarily determined by genetic predisposition, or socioeconomic and psychological factors lead an individual to try and then later to use drugs compulsively. Risk factors for heavy, dependent drug use are much more significant when they occur together rather than individually.

A defining characteristic of drug dependence is that drug use begins as a voluntary action to seek a rewarding stimulus, but continued use results in loss of control over the use, despite its negative consequences (Dackis & O'Brien, 2005). The effects of many illicit drugs are mediated via various brain circuits, in particular the mesolimbic systems, which have evolved to respond to basic rewards (such as food and sex) to ensure survival. A diverse range of substances, including opioids, stimulants and cannabis, as well as alcohol and nicotine, all appear to produce euphoric effects via increasing levels of dopamine (a neurotransmitter) in the nucleus accumbens (Dackis & O'Brien, 2005). This has been well demonstrated in human brain-imaging studies (Volkow *et al.*, 1999). Euphoria resulting from use then potentiates further use, particularly for those with a genetic vulnerability (see below). Chronic drug use may produce long-lasting changes in the reward circuits, including reductions in dopamine receptor levels (Volkow *et al.*, 1999), and these contribute to the clinical course of drug dependence, including craving, tolerance and withdrawal (Lingford-Hughes & Nutt, 2003). In addition, other types of neurotransmitter systems (for example, opioids, glutamates and cannabinoids) are implicated in the misuse of specific drugs.

Although initiation into drug use does not lead inevitably to regular and problematic use for many people (Anthony *et al.*, 1994). It is clear that when use begins, it often escalates to misuse and sometimes to dependence (tolerance, withdrawal symptoms and compulsive drug taking). Once dependence is established, particularly with opioids, there may be repeated cycles of cessation and relapse extending over decades

(National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). Vulnerability to use is highest among young people, with most problem heroin users being initiated before the age of 20. Individuals dependent on drugs often become so in their early twenties and may remain intermittently dependent for many years.

The neurobiological account of fundamental reward systems implicated in drug misuse may parallel the sociocultural–behavioural–cognitive model presented by Orford (2001). He conceptualised drug misuse as an 'excessive appetite', belonging to the same class of disorders as gambling, eating disorders and sex addiction. All involve activities that form strong attachment, and were once rewarding, but with excessive consumption result in compulsion and negative consequences. Orford argued that the emotional regulation of such appetitive behaviours in their respective social contexts (for example, the excitement associated with gambling or the anticipation of the next 'fix' of heroin), well characterised within the principles of operant conditioning, is a primary factor driving excessive use. Secondary factors such as internal conflict (knowing that the behaviour is harmful yet being unable to disengage from it) potentiate these emotions and thus excessive use, but an alternative result is that the individual alters behaviour in order to resolve such conflict. This crucially suggests that recovery is not impossible, but also that successful treatment attempts are likely to operate against a background of powerful natural processes (Orford, 2001).

3.4 THE COURSE OF DRUG MISUSE

Drug misuse is a relapsing and remitting condition often involving numerous treatment episodes over several years (Marsden *et al.*, 2004). While the initiation of drug use does not lead inevitably to dependence over the long term (Anthony & Petronis, 1995), a number of factors can potentiate this developmental course. Earlier initiation of drug use increases the likelihood of daily use, which in turn results in a greater likelihood of dependence (Kandel *et al.*, 1986).

Among people who misuse opioids, who form the predominant in-treatment population in the UK, most individuals develop dependence in their late teens or early twenties, several years after first using heroin, and continue using over the next 10–30 years. In a long-term outcome study (up to 33 years) of 581 male opioid users in the USA, 30% had positive (or refused) urine tests for opioids, 14% were in prison and 49% were dead (Hser *et al.*, 2001). Longitudinal data from the US also showed that the average time from first to last opioid use was 9.9 years, with 40% dependent for over 12 years (Joe *et al.*, 1990). Although it is the case that problem drug users can cease drug use without any formal treatment (Biernacki, 1986), for many it is treatment that alters the course of opioid dependence.

Although drug misuse can affect all socioeconomic groups, deprivation and social exclusion are likely to make a significant contribution to the maintenance of drug misuse (ACMD, 1998).

Factors that influence the cessation of drug use in adulthood are similar to those associated with lack of drug use in adolescence. For example, transitions into social

roles with greater conventionality, responsibility and/or contexts that are not favourable to using drugs (such as employment, mortgage, marriage and pregnancy; for example, Bachman *et al.*, 1997), and good health are not associated with long-term use. Peer pressure is a major influence on experimental use and is also likely to affect a move towards regular use. The level of drug use is again a predictor of continued use.

Once an individual is dependent, drug use is generally a chronic condition, interspersed with periods of relapse and remission (Marsden *et al.*, 2004). Repeated interaction with the criminal justice system, long-term unemployment and increasing social isolation serve to further entrench drug use.

3.5 THE PHARMACOLOGY OF OPIOIDS

Opioids have many effects on the brain, mediated through specific receptors (μ, κ, or δ). The key opioid receptor subtype is μ, which mediates euphoria, as well as respiratory depression, and is the main target for opioids (Lingford-Hughes & Nutt, 2003), while the κ receptor is involved in mood regulation. Drugs such as heroin and methadone are agonists, which stimulate the receptor. Buprenorphine is a partial agonist; that is, it occupies the receptor in the same way but only partially activates it. In addition, it is an antagonist at the κ receptor and therefore is less likely to lower mood compared with μ agonists.

Soon after injection (or inhalation), heroin metabolises into morphine and binds to opioid receptors. This is subjectively experienced as a euphoric rush, normally accompanied by a warm flush, dry mouth, and sometimes nausea, vomiting and severe itching. As the rush wears off, drowsiness, and slowing of cardiac function and breathing (sometimes to the point of death in an overdose), persist for several hours (National Institute on Drug Abuse [NIDA], 2005a). The effects of methadone are similar but more drawn out and therefore less intense (lasting up to 24 hours when taken orally as prescribed); however, this may be circumvented by illicit users who inject the drug.

3.6 THE PUBLIC HEALTH IMPACT OF DRUG MISUSE

The most obvious consequence of long-term illicit opioid use is the development of opioid dependence itself, and the associated harms. These include: increased mortality from overdose and from other directly or indirectly associated harms such as increased risk of infection with blood-borne viruses (HIV, hepatitis B and hepatitis C); high levels of depression and anxiety disorders; social problems such as disrupted parenting, employment and accommodation; and increased participation in income-generating crime.

Mortality, particularly in heroin-dependent users, is high, with estimates of between 12 (Oppenheimer *et al.*, 1994) and 22 times (Frischer *et al.*, 1997) that of the general population. In England and Wales, there were 1,382 drug-related deaths in 2005 (National Programme on Substance Abuse Deaths, 2005). The majority (59%) were cases of accidental poisoning, although a sizeable proportion (16%) was a result

of intentional self-poisoning. Opioids (alone or in combination with other drugs) accounted for some 70% of the deaths, and cocaine 13%. Many of the deaths appear to be due to multiple drug toxicity, especially the presence of central nervous system depressants (for example, alcohol and benzodiazepines), rather than simply an 'overdose' of an opioid. This is supported by research that shows those whose deaths were attributed to overdose have opioid levels no higher than those who survive, or than heroin users who die from other causes (Darke & Zador, 1996). Recent cohort studies have shown that mortality rates from methadone-related death are decreasing (Brugal *et al.*, 2005).

Repeated injection will have medical consequences, such as scarring, infection of blood vessels, abscesses, and compromised functioning of the kidney, liver and lungs (with increased vulnerability to infections). HIV infection is a major problem for injecting drug users, with the number of new diagnoses of HIV in the UK holding at around a hundred for the last few years, and 5.6% of all UK diagnoses attributed to injecting drug use by the end of 2005 (Health Protection Agency *et al.*, 2006). There are differences in geographical distribution of HIV in the UK, with rates higher in some centres such as London. Approximately 50% of injecting drug users have been infected with hepatitis C, but this rate, like the HIV prevalence rate, is lower than in many other countries (Health Protection Agency *et al.*, 2006). Transmission of both hepatitis A and B continues, even though there are effective vaccines. Needle and syringe sharing increased in the late 1990s and since then has been stable, with around one in three injecting drug users reporting this activity in the last month (Health Protection Agency *et al.*, 2005).

Psychiatric comorbidity is common in drug misuse populations, with anxiety and depression generally common, and antisocial and other personality disorders in opioid-using populations (Regier *et al.*, 1990, 1998). The national US Epidemiological Catchment Area study of the prevalence of mental health disorders reported a 47% lifetime prevalence rate of substance misuse (drugs and alcohol) among people with schizophrenia compared with 16% in the general population, and found that more than 60% of people with a diagnosis of bipolar I disorder had a lifetime diagnosis of substance misuse disorder. Around one in five of the people in the NTORS sample had previously received treatment for a psychiatric health problem other than substance misuse (Marsden *et al.*, 2000). Drug misuse disorders complicated by other comorbid mental disorders have been recognised as having a poorer prognosis and being more difficult to treat than those without comorbid disorders; comorbid disorders are more likely to be chronic and disabling, and result in greater service utilisation.

Lost productivity and unemployment increase with the severity and duration of drug misuse, and personal relationships are placed under considerable strain by dependent drug use. Problems with accommodation are also common in such groups. For example, prior to intake in the NTORS, 7% of the study group were homeless and living on the street, 5% were living in squats and 8% were living in temporary hostel accommodation (Gossop *et al.*, 1998).

Drug misuse may also have a negative impact on children and families (see section 3.12). In the UK it is estimated that 2–3% of all children under the age of 16 years have parents with drug problems (ACMD, 2003). While use of opioids

does not necessarily impact on parenting capacity, registration on UK child protection registers for neglect has been correlated strongly with parental heroin use, and parental problem drug use has been shown to be one of the commonest reasons for children being received into the care system (Barnard & McKeganey, 2004).

3.7 IDENTIFICATION AND ASSESSMENT OF DRUG MISUSE

So prevalent is drug use that all healthcare professionals, wherever they practice, should be able to identify and carry out a basic assessment of people who use drugs. Many people who misuse drugs do not present to drug treatment services, with perhaps 50% not seeking treatment; however this represents a significant improvement on the position in the UK in the early 1990s, when perhaps only 20% of people who misused drugs sought treatment. Of those who do not seek treatment for their drug misuse, a proportion may nevertheless present to other medical services, the criminal justice system and social care agencies. Many will not be seeking help for their drug problems and many, for example some of those primarily misusing cocaine or cannabis, may not be aware of the potentially harmful effects of their drug use. It is probable that those who present to services for drug treatment have the greatest number of problems (Best *et al.*, 2006b).

Routine screening for drug misuse is largely restricted in the UK to criminal justice settings, including police custody and prisons (Matrix Research and Consultancy & National Association for the Care and Rehabilitation of Offenders [NACRO], 2004); it is sparsely applied in health and social care settings. For example, a recent study of psychiatric inpatients in London found that only 1 in 50 people admitted to hospital had undergone screening for drug misuse (Barnaby *et al.*, 2003). The NTA's updated Models of Care service framework emphasises the importance of non-specialist (tier 1) services in the identification of drug misuse as a precursor to referral for treatment (NTA, 2006). Opportunistic methods for the effective identification of drug misuse should therefore be considered in a variety of healthcare settings. These are described in more detail in the NICE clinical guideline *Drug Misuse: Psychosocial Interventions* (NICE, 2007).

For those identified and considering treatment, a good assessment is essential to continuing care. Assessment skills are important across all health and social care professionals who may come into contact with drug misuse. Assessment includes information about past and current drug use (amount, type, duration, periods of abstinence and effect of abstinence), history of injecting, risk of HIV and other bloodborne viruses, medical history, forensics and previous contact with treatment services. Assessment is a continuous process carried out at every contact with the individual and his or her healthcare professional, counsellor or social worker and can take place over many years. Urine testing for the absence or presence of drugs is an important part of assessment and monitoring. Formal rating scales may be helpful in assessing outcomes and in certain areas of monitoring, for example of withdrawal symptoms.

The aims of assessment are: to confirm drug use (history, examination and urinalysis); assess the degree of dependence; identify complications of drug misuse and

assess risk behaviour; identify other medical, social and mental health problems; determine the expectations of treatment and the degree of motivation to change; assess the most appropriate level of expertise required; determine the need for substitute medication; and refer to/liaise appropriately with shared care, specialist or specialised generalist care, or other forms of psychosocial care where appropriate. In addition, immediate advice on harm minimisation, including, if appropriate, access to sterile needles and syringes, as well as testing for hepatitis and HIV, and immunisation against hepatitis, should take place.

3.7.1 Clinical practice recommendations

3.7.1.1 Detoxification should be a readily available treatment option for people who are opioid dependent and have expressed an informed choice to become abstinent.

3.7.1.2 People who are opioid dependent should be given the same care, respect and privacy as any other person.

3.7.1.3 In order to obtain informed consent, staff should give detailed information to service users about detoxification and the associated risks, including:

- the physical and psychological aspects of opioid withdrawal, including the duration and intensity of symptoms, and how these may be managed
- the use of non-pharmacological approaches to manage or cope with opioid withdrawal symptoms
- the loss of opioid tolerance following detoxification, and the ensuing increased risk of overdose and death from illicit drug use that may be potentiated by the use of alcohol or benzodiazepines
- the importance of continued support, as well as psychosocial and appropriate pharmacological interventions, to maintain abstinence, treat comorbid mental health problems and reduce the risk of adverse outcomes (including death).

3.7.1.4 All interventions for people who misuse drugs should be delivered by staff who are competent in delivering the intervention and who receive appropriate supervision.

3.8 THE AIMS OF THE TREATMENT AND MANAGEMENT OF DRUG MISUSE

The clinical management of drug misuse may be categorised into three broad approaches: harm reduction, maintenance-oriented treatments and abstinence-oriented treatments. Detoxification is often seen as the first stage in the process of achieving abstinence. All treatments aim to prevent or reduce the harms resulting from use of drugs. Care planning and keyworking should form a core part of subsequent treatment and care.

Harm reduction aims to prevent or reduce negative health or other consequences associated with drug misuse, whether to the drug-using individual or, more widely, to society. With such approaches, it is not essential for there to be a reduction in the drug use itself (although, of course, this may be one of the methods of reducing harm). For instance, needle and syringe exchange services aim to reduce transmission of blood-borne viruses through the promotion of safer drug injecting behaviour.

Maintenance-oriented treatments in the UK context primarily refer to the pharmacological maintenance of people who are opioid dependent, through the prescription of opioid substitutes (methadone or buprenorphine). This therapy aims to reduce or end their illicit drug use and the consequential harms.

Abstinence-oriented treatments aim to reduce an individual's level of drug use, with the ultimate goal of abstinence. The NTORS found that approximately one third of those entering treatment services were abstinent 5 years later (Gossop *et al.*, 2003). However, these treatments may be associated with an increased risk of death from overdose in the event of relapse after a period of abstinence, during which time drug tolerance is lost (Verger *et al.*, 2003). Consequently, it is particularly important for abstinence-oriented treatment to include education on post-detoxification vulnerability to relapse (Gossop *et al.*, 1989) and to overdose, and for wider psychosocial rehabilitation support to be provided.

Detoxification refers to the process by which the effects of opioid drugs are eliminated from dependent opioid users in a safe and effective manner, such that withdrawal symptoms are minimised (WHO, 2006). With opioids, this process may be carried out by using the same drug or another opioid in decreasing doses, and can be assisted by the prescription of adjunct medications to reduce withdrawal symptoms (DH, 1999). The pharmacological process of detoxification is the first stage of achieving abstinence, with the primary aim to provide symptomatic relief from withdrawal while physical dependence on the drugs is being eliminated (Anglin & Hser, 1990); this should be an active process carried out following the joint decision of the service user and clinician, with adequate planning for or provision of aftercare. Opioid detoxification takes place in a variety of settings, including the community, inpatient units, residential units and prisons, and at different rates.

Care planning should consider the following when any treatment or management plan is developed:

- type and pattern of use
- level of dependence
- comorbid mental and physical health problems
- setting
- age and gender
- service users' aspirations and expectations.

The general principles of treatment are that no single treatment is appropriate for all individuals, treatments should be readily available and begin when the service user presents, and there should be the capacity to address multiple needs. It is also accepted that treatments will change over time. It appears that treatment does not need to be voluntary to be successful – comparisons of voluntary and legally coerced drug treatment have been reviewed recently elsewhere (NCCMH, 2008). For most

people in long-term treatment, that is those with opioid dependence, substitute medications, such as methadone and buprenorphine, are important elements of care. However, services also need to address coexisting problems, such as mental health and physical health problems, alongside the drug misuse.

Keyworking forms the core part of treatment for most service users with long-term drug misuse problems (NTA, 2006). Typically, this involves the following:

- conducting an assessment of need (and a risk assessment)
- establishing and sustaining a therapeutic relationship
- clarification of the service user's goals in relation to his/her drug use
- discussion, implementation, evaluation and revision of a treatment plan to address the client's goals and needs
- liaison and collaboration with other care providers
- integration of a range of interventions based on a biopsychosocial model of drug use (for example, prescribing, addressing needs such as housing and improving personal relationships)
- use of one or more techniques derived from one or more therapeutic models to engage and retain the service user in treatment and to support the treatment plan (for example, drug diaries and motivational skills) in the absence of delivering a complete course of formal psychological therapy.

3.8.1 Clinical practice recommendations

3.8.1.1 Service users should be offered advice on aspects of lifestyle that require particular attention during opioid detoxification. These include:

- a balanced diet
- adequate hydration
- sleep hygiene
- regular physical exercise.

3.8.1.2 Staff who are responsible for the delivery and monitoring of a care plan should:

- develop and agree the plan with the service user
- establish and sustain a respectful and supportive relationship with the service user
- help the service user to identify situations or states when he or she is vulnerable to drug misuse and to explore alternative coping strategies
- ensure that all service users have full access to a wide range of services
- ensure that maintaining the service user's engagement with services remains a major focus of the care plan
- review regularly the care plan of a service user receiving maintenance treatment to ascertain whether detoxification should be considered
- maintain effective collaboration with other care providers.

3.8.1.3 In order to reduce loss of contact when people who misuse drugs transfer between services, staff should ensure that there are clear and agreed plans to facilitate effective transfer.

3.9 THE DEVELOPMENT OF DETOXIFICATION SERVICES

As stated above, opioid detoxification is the first stage in the process of achieving abstinence, with the primary aim of providing symptomatic relief from withdrawal while physical dependence on the drugs is being eliminated (Anglin & Hser, 1990). Opioid withdrawal includes a variety of symptoms: anxiety, tremors, nightmares, insomnia, weight loss, nausea, vomiting, seizures and delirium (for example, Bradley *et al.*, 1987). The process of detoxification alone is not perceived as a solution for long-term abstinence (Lipton & Maranda, 1983). Indeed psychosocial interventions should be delivered concordantly in order to maximise benefits derived from detoxification and to address wider issues surrounding drug use. If these are not delivered, benefits from detoxification may only be temporary, and the intervention could be ultimately unsuccessful (Hanson *et al.*, 2006). Detoxification from opioids takes place in a variety of settings, including the community, inpatient units, residential units and prisons. The context in which it is delivered will depend on the nature of the drug itself and the severity of dependence.

Methadone, the most widely used opioid agonist in assisted detoxification (Jaffe, 1989), was developed in Germany during the second world war, when morphine was unavailable. During the post-war period, methadone was primarily used in hospital settings to detoxify dependent opioid users (Gerstein & Harwood, 1990). The aim of using methadone to detoxify heroin users is to suppress withdrawal symptoms through the provision of an opioid-based substitute medication. Service users are initially provided with a dose of methadone equivalent to their illicit opioid (heroin) use, and doses are gradually lowered until they are opioid free. The most rapid regimes take 7–21 days, while 'slow tapering' regimes may take up to 6 months or longer (DH, 1999), depending on what is judged to be most appropriate by the practitioner and service user. Methadone does not deliver the intense euphoric 'high' associated with heroin, and also has a longer half-life, meaning that it remains in the body for longer than heroin; while the effects of heroin wear off in 2–3 hours, the effects of oral methadone continue for 12–24 hours. Therefore, methadone dose reductions are relatively easy to achieve in the initial phase of a detoxification programme, but during the latter stages withdrawal symptoms may become more prominent and harder to manage. These concerns have led to the use of alternative detoxification agents such as clonidine, lofexidine, buprenorphine and dihydrocodeine.

Like methadone, buprenorphine is a synthetic opioid that acts as a substitute for heroin. It was licensed for use for opioid dependence treatment in the UK in 1999, and thus it is not as well established as other detoxification treatments (Lintzeris *et al.*, 2002). Buprenorphine is a partial opioid μ agonist, which occupies receptors without fully activating the system, and is therefore associated with a less severe withdrawal syndrome (Ford *et al.*, 2004). In comparison with methadone, buprenorphine also has a longer duration of action, and an increased safety profile in overdose due to its lesser effects (Walsh *et al.*, 1994).

Alpha$_2$ adrenergic agonists, which include clonidine and lofexidine, are known to ameliorate a cluster of opioid withdrawal symptoms (those associated with the noradrenaline system, including sweating, shivering, and runny nose and eyes). Clonidine,

originally developed as an anti-hypertensive drug, had received widespread use as one of the first non-opioid-based options for managing opioid withdrawal (Gossop, 1988), but its hypotensive effects are problematic in the context of detoxification. Lofexidine was therefore developed as an alternative to clonidine with reduced hypotensive effects, and is currently licensed and used widely in the UK for opioid detoxification. Whilst alpha$_2$ adrenergic agonists allow for detoxification to be attained over a shorter length of time (typically ranging from 5–7 days) compared with buprenorphine, they do not address other (non-noradrenergic) withdrawal symptoms, and therefore must be supplemented by additional medications.

Problems commonly associated with detoxification are low completion rates and high levels of relapse post treatment (Mattick & Hall, 1996). In an attempt to address this issue, ultra-rapid detoxification techniques using naltrexone administered under anaesthesia or deep sedation within a medically monitored setting have been established in recent years (Loimer *et al.*, 1991). Naltrexone is a long-acting opioid antagonist, first approved for use in 1984 as a maintenance treatment to block the effects of opioids after detoxification (Tai & Blaine, 1997). When used in the context of opioid detoxification, it displaces any opioids that are already present in the drug user's system, thereby precipitating withdrawal.

Service users undergoing ultra-rapid detoxification are typically admitted to the intensive care unit of a hospital or a high dependency unit for 24 hours, during which time naltrexone and/or naloxone is administered to precipitate withdrawal. On presentation of withdrawal symptoms, the service user is anaesthetised or heavily sedated, such that (in theory) he or she does not consciously experience any of the ensuing acute withdrawal symptoms. A significant number of adjunct medications, such as antidiarrhoeals, antiemetics, alpha$_2$ adrenergic agonists and benzodiazepines, are also administered to manage withdrawal symptoms. There is no uniformity in methods employed to carry out ultra-rapid detoxification, and there has been much controversy surrounding their safety, cost and effectiveness due to the limited long-term outcome data (Strang *et al.*, 1997a). Ultra-rapid detoxification is currently not used in the NHS.

3.10 CURRENT CARE AND TREATMENT IN THE NHS

The British response to drug problems dates back to the report of the Rolleston Committee of 1926. The committee accepted dependence as a disease and established a medical approach to drug problems in Britain rather than the predominantly punitive one pursued in other countries such as the US. Rolleston gave doctors a large degree of clinical freedom in their response to people who were dependent, including the use of maintenance treatment. To this day, maintenance is considered an essential aspect of drug treatment.

A large increase in the number of people with heroin dependence in Britain in the mid-1960s prompted the establishment of a network of drug dependence clinics set in psychiatric hospitals and run directly by the NHS. The second epidemic of heroin use in the early 1980s led to a further re-shaping of the British treatment response. A multidisciplinary approach was encouraged through the establishment of community

drug teams and attempts to increase general practitioner (GP) involvement in drug treatment, with the first in a series of clinical guidelines setting out the responsibilities of the prescribing doctor (DH, 1999). The guidelines also sought to encourage shared care of the person who misuses drugs by different professional groups. While the drug dependence clinics remained the cornerstone of this reshaped approach, the vast majority of treatment prescriptions, namely oral methadone, were now dispensed by community pharmacists and consumed at home. This was further supported by the 2004 General Medical Services contract provision for enhanced maintenance prescribing services (British Medical Association, 2004).

The emergence of HIV/autoimmune deficiency syndrome (AIDS) in the 1980s led to the introduction of needle and syringe exchange schemes as an addition to the treatment services available. These schemes provided needles and syringes to the dependent and non-dependent injector. Harm reduction also became an important aspect of treatment responses to drug misuse. Another refocusing of drug treatment came in the 1990s, with increased concern over the link between criminal activity and drug misuse. Criminal justice settings were seen as an important conduit for getting people who misuse drugs into treatment and a number of interventions such as Drug Treatment and Testing Orders (DTTOs) were established. In 2003, the Home Office, with the DH and the NTA as its key partners, introduced the Drug Interventions Programme (DIP), which seeks to bring treatment and criminal justice services together in responding to drug misuse (Witton *et al.*, 2004).

Most drug treatment is initiated as a result of drug users themselves seeking treatment. However, there has recently been a rapid expansion in forms of legally coerced treatment, whereby the person who misuses drugs is coerced into treatment as an alternative or adjunct to criminal sanctions (Wild *et al.*, 2002). Such treatment may be legally ordered by the court or through referral away from the judicial process, usually following arrest and charge for drug-related and other offences. Despite recent policy shifts of referral away from the courts, however, many people who misuse drugs still serve prison sentences. A recent estimate suggests that around 39,000 prisoners with a serious drug problem are in custody at any one time (All-Parliamentary Group on Prison Health, 2006). Within the prison setting, drug misuse treatment is increasingly being offered following a number of recent developments, including the phased transfer of responsibilities for commissioning healthcare in publicly funded prisons from the Home Office to the NHS (DH, 2006). While the mainstay of treatment in prison has traditionally been one of detoxification upon admission, there has been a recent policy shift allowing increased access to opioid maintenance therapy and psychosocial interventions.

Current practice in detoxification

Much of the current treatment of drug misuse in services directly provided or purchased by the NHS focuses on the treatment of opioid misuse. In large part this is reactive to the drug problems with which service users present, who may themselves be informed by awareness of relevant treatments as well as their own perceptions of whether their drug use is problematic. In the last decade there has been a significant increase in the numbers of service users being treated in primary care settings, with a

national survey showing that in 2001 almost three times as many GPs were seeing people who misused opioids compared with in 1989 (Strang *et al.*, 2005). GPs are now a large part of the substance misuse workforce. Much of the change in the response from primary care has been through initiatives from the Royal College of General Practitioners, for example the development of a national drugs training programme and the creation of a national primary care network.

Around 30,000 detoxifications are currently carried out each year, and the majority are in the community; among individuals who have received any form of treatment for drug misuse, 19% had previously undergone community detoxification while 13% had received residential treatment (Best *et al.*, 2006a). Approximately one third entering treatment services generally are abstinent 5 years later (at least for a period of time) (Gossop *et al.*, 1998).

Service users consulting either a GP or a community drug team are assessed initially and their plans for treatment elicited. One of the dilemmas of drug treatment is that the majority of heroin users – as high as 81% according to the NTA Annual User Satisfaction Survey – wish to become drug free (Best *et al.*, 2006a), hence they may frequently ask for detoxification. This is often unrealistic as there may be many factors that make abstinence unlikely to be possible for the individual at that time. These would include drug-related risk factors such as polysubstance use and social risk factors such as homelessness. The availability of treatment options for detoxification may also be limited by external factors, in particular for inpatient detoxification. Thus the process of treatment planning is often one of negotiation and education, with the treatment provider having to give the service user realistic information about outcomes and the possible range of treatment options.

In practice, this means that most service users only commence formal detoxification following a period of stabilisation on a substitute opioid (either methadone or buprenorphine). The stabilisation results in the cessation of illicit drug use, with the individual feeling comfortable on the dose of substitute opioids he or she is taking. This process can take months or even years to achieve and for many only happens after years of maintenance treatment.

Once a prescriber and a service user have planned a detoxification, the rate and nature of the dose reductions are agreed in advance, although they can be revised. The service provider should provide a package of psychosocial support, which is usually delivered via a keyworking relationship which may or may not be with the prescriber. The prescriber and service user also need to agree on a package of aftercare to support the service user after the pharmacological phase of treatment is finished.

For a service user in the community who is seriously committed to detoxification treatment, dose reduction can take place over anything from a few days to several months, with a higher initial stabilisation dose taking longer to taper. In practice, up to 3 months is typical for methadone reduction, while buprenorphine reductions are typically carried out over 14 days to a few weeks. Detoxification using lofexidine is much faster than using either methadone or buprenorphine, typically lasting 5–7 days, and up to a maximum of 10 days.

Although a substantial number of service users benefit from detoxification in the community, many who start these programmes may fail because they start to use

illicit drugs when their substitute opioid dose is reduced. The programme can then be changed to maintenance by increasing the dose again and changing the treatment plan to address other issues. Unfortunately this can result in service providers having treatment plans with unclear treatment goals.

Service users on maintenance programmes often also reduce their doses over time. If they are otherwise stable, this can be successful but it may be very slow; indeed, dose reductions may be planned over many years. These gradual dose reductions are not really detoxifications; clinical experience would indicate that this approach may be successful but there is little research evidence to support it. In practice, a gradual dose reduction may prepare a service user for detoxification.

Detoxification in an inpatient setting can take place over a shorter time than in the community as the supportive environment helps a service user to tolerate emerging withdrawal symptoms. However, a similar process occurs as in the community: that of stabilisation on the dose of a substitute opioid and then gradual dose reduction. In an inpatient environment, reduction typically takes place over a shorter time: 14–21 days for methadone and 7–14 days for buprenorphine.

Various rapid detoxification programmes involve the use of naltrexone and other adjuncts (see above) to accelerate the pharmacological process of detoxification to as short as 24 hours, but these are not currently available in the NHS.

Service users who are incarcerated are often detoxified in prison. Historically this has been done involuntarily, although increasingly maintenance is available to service users who are eligible. Also, historically, service users have had no choice about the drugs used for their detoxification but again this is beginning to change. It is also important to remember that, despite the involuntary nature of prison detoxification, many inmates regard a detoxification in prison as welcome and a chance to reduce their drug use either temporarily or indeed permanently.

3.11 THE EXPERIENCE OF DRUG MISUSE – PERSONAL PERSPECTIVES

3.11.1 Testimony A

My first experience of taking drugs was at senior school. One of my school friends had started smoking cannabis and tried to assure me that it was harmless. After building up the courage, I half pretended to take a few puffs to test the ground. After this experience, I discovered that one of my teachers smoked cannabis too. Sometimes I would go to the pub at lunchtime, have a pint (in the same pub as the teachers) and a joint, then maybe go back to school if I didn't get too wrecked. For the last year of school, I experimented with so many drugs that I never attended and, when it came to leaving, the teachers didn't know who I was.

Along with alcohol and cannabis, I discovered that pills seemed to take me away from my boredom and depression. My mother had a stock of them in the cupboard and I soon discovered which pills were which and that diazepam and chlordiazepoxide seemed to do the trick. Not long after this, I met lots of people who mainly smoked

dope but were also buying different drugs. In those early days, there were all kinds of uppers and downers, either acquired from people's families or stolen from chemists, such as 'reds' and 'browns', 'clears', 'black bombers', 'purple hearts', dextroamphetamine, and so on. I experimented with just about everything I could get my hands on, from speed, LSD [lysergic acid diethylamide] and mushrooms, to dextromoramide, secobarbital, diazepam, dipipanone and methaqualone.

I was about 16 when I first realised I had a problem: I wanted to stay permanently stoned from whatever drugs I could get my hands on. I usually always had cannabis to enhance the feeling of other substances.

I was 16 or 17 when I was introduced to heroin. I would go to a friend's house on a regular basis and smoke dope until I changed colour; one day I went and was offered heroin. I remember my friend saying: 'Look, all of us have had it and we are fine'. Even though I had fears about becoming addicted on the first go, I tried it and loved it. All of my true friends warned me against it and what would happen, but I just had to see for myself. Little did I know that it was going to cost me 23 years of my life, and that I would have no friends left. Even though I knew lots of other people who took drugs, I felt very isolated; I didn't even feel equal to someone who had a different addiction to me. I felt the lowest of the low for many years and felt so tightly trapped in my heroin addiction that I truly believed I would only ever come out of it dead. Some people accept that lifestyle and others hate it. I was one of those who hated it but could never see an end to it no matter how hard I tried. I was depressed as a child, which became more severe and hard to handle as my addictive years went by. I twice came to the point of taking my own life and at the last second couldn't do it. I also thought about it more times than I can remember, just wishing I could have been dead.

My mother feared she would be getting a phone call any time to tell her that her son was dead. I believe my drug use affected my mother's health because she was always worrying about me. My sister thought I was a waste of time and at one point my father disowned me. I moved away from my home town to London in 1982 in an attempt to give up heroin. Since then, I have never moved back home; I wanted to try to hide as much of my addiction as I could from my family.

Any relationships I had while using heroin inevitably didn't last very long. Being an addict, I lied a lot about where I was going and what I was doing. Methadone made things a little more stable, but needless to say, sex wasn't as regular as it should have been. One or two ex-partners actually thought I had a mistress; they were right: 'Lady Heroin'.

I was first treated for drug addiction in the psychiatric unit of my local hospital in 1980. I entered a detox programme and was prescribed methadone but I was not offered any counselling. When I came out, I started using again. After this, I was in and out of prison for drug-related offences, but I was offered no treatment inside; when it looked like I was going to prison for a third time, I decided I needed help. Instead of receiving a third prison sentence, I asked the judge if I could go into residential rehab in London. I felt safe in rehab and didn't realise how little I had to look forward to once completing and leaving rehab. I eventually went back on heroin again. For a time, I was prescribed physeptone and pure heroin ampoules but without much in the way of counselling.

It wasn't until 1985 that I saw a counsellor (in order to get methadone from a community treatment programme you had to see a counsellor twice or three times a week). My relationships with professionals were not particularly good. I resented the fact that I had to do what my keyworker said or be thrown off my course. Once I had finished one course of 6-week reduction, I went back on the waiting list for another one. You were deemed to have failed if you wanted to go on another course. It took years before I began to trust any of the workers. For over 2 and a half months I was refused a place for community treatment due to false positive urine tests; the tests said that I had diazepam in my system when I really hadn't taken anything.

I was also offered treatment, from a little help at home with a dihydrocodeine from a sympathetic doctor, to a detox at home with lofexidine after being monitored for blood pressure for a couple of hours.

During this period of my life I was on heroin for most of the time with brief periods of taking methadone. I had no life at all, except the routine of waking up, looking for money to buy heroin, and then buying heroin.

But in 2003 I decided that I wanted to stop using for good; I felt like it was 'wake-up or die' time. One of the main reasons I wanted to stop was because heroin suppressed just about all of my emotions and I desperately wanted to feel something again. Without emotions I had no incentive to drive a car, love a woman, get a house, fly a kite; without emotions I was a zombie. I was living with someone at the time who used to go out every day and do all the scheming for money for drugs. But I wasn't going to put my neck on the line any longer by risking going to prison, so the day he left I knew was the day I was going to give up for good. Without support from a drug worker, I stopped using heroin and 2 days later started taking buprenorphine, which to my mind is a godsend; on the third day, I was up and about, helping deliver 7 tonnes of food aid and feeling great. Since that day I have not wanted to take heroin at all.

After 23 years, I had stopped using drugs. It had been a relatively simple process and I wondered why it could not have happened before. But it hadn't happened, probably because I had not been able to break the cycle before. I realised that this was the time that one big window of opportunity was opening; but, without doing something to keep me occupied, I knew there was every chance of slipping backwards.

I found a crumbling self-help group with one person attending and one part-time staff member; we managed to bring that group back to life. I spent the next 2 and a half years volunteering support to others who wanted to use self-help. I've also had lots of input into my local addiction organisations as well as national input; this in turn helped me to help myself.

Since this time, I've never looked back. I've had so much energy and time to start enjoying it all. Life is radically different: buprenorphine, which I take daily, has helped me gain stability and self-respect. I no longer have the worry of being in and out of prison because I don't need to go out on the streets looking for money for heroin. And, thanks to buprenorphine, I really don't have any craving for heroin. I am now thinking about stopping taking buprenorphine.

Since stopping using drugs, I still get depression but it's much easier to handle and much less frequent. I can sometimes feel depressed for days on end, but usually all I

need to do is think about the desperation I felt from 23 years of using; I then just make a simple comparison.

The drug use has taken its toll on my physical health. I had a blood test after I stopped taking heroin and found out that I have hepatitis C. The doctor didn't give me any sympathy and told me that I can expect to be dead within 30 years after my liver becomes cancerous. I still have the virus, which hasn't got any worse over the years, but I am giving some thought to having it treated soon.

I didn't learn lessons I should or could have while using, but now with clarity of mind, one of the many lessons I've learned is that it will pass, but if any window of opportunity opens before it does pass, I take it.

Since I first started using, I think that overall the whole of the field of care has changed for the better. I believe that listening to addicts' and ex-addicts' views on treatment has reformed drug treatment services nationwide. Many more doctors have become involved with community treatment and, from my experience, really do care.

3.11.2 Testimony B

I witnessed drug and alcohol misuse very early on in my life, either through relatives who openly smoked cannabis in front of me, or simply by being present at drinking parties in my home, but my own first-hand experience of illicit drugs began when I was 11 years old. I had just started senior school and I knew that drugs were available there, due to the fact that I had cousins at the school who used drugs. Soon after starting senior school, I was associating with older pupils; after school at a friend's house, we inhaled some poppers (amyl nitrate) that my friend had stolen from his aunt, but I didn't really like the experience. Shortly after that, we used our dinner money to buy a small amount of hash from one of my cousins. We smoked a spliff during the lunch break, and I was so smashed that I couldn't go back to school.

After this experience, I smoked cannabis as often as I could afford, but I used to read up on all the different drugs and their effects, and what I really wanted to try out was LSD, which during that time was in plentiful supply, and also at a relatively low price. Before long, I had found someone prepared to sell me acid on a regular basis. Following this experience, I then moved on to just about all of the other drugs available at that time, and by the age of 14, I was selling drugs in and outside school. Eventually, I was expelled from school for selling drugs, non-attendance and disruption. No charges were brought, but I acquired a label as someone who could be approached for drugs.

I realised very early on during my substance misuse that I had a problem. At the time, I couldn't admit, or in some cases fully comprehend, some of the reasons why I used drugs and drank alcohol, although now that I look back, I am able to identify the reasons. It would be difficult to provide a summary-like version of the antecedents to my drug use and criminality, except to say that I felt the need to opt out of reality. I definitely knew I had a problem because I could see that my habits were different from other people's. Most people with whom I took drugs would all gather round at one of our houses; then, at a particular time, they would have to go home, as they were expected to, because they had to be at school. However, I didn't, so I would then go

on to an older person's house, where I would take more amphetamine, smoke cannabis all night and drink. Very quickly, my circle of 'friends' was reduced to people who were similar to me. I used to stay awake for days at a time, and the majority of people who I came into contact with were just buying drugs from me. During this time, despite the fact that I was still enjoying taking certain drugs, I led a lonely, maladjusted life. I used to take such large amounts of drugs (several types at once) that I'd experience many unpleasant effects; my health began to suffer at an early age, and I later contracted hepatitis C. I had become addicted, was surrounded by drugs, had become accustomed to a particular lifestyle and, above all, didn't feel able or ready to even contemplate a life without drugs.

My drug use devastated my family, and my family's drug use devastated me. (My mother didn't use drugs, although she is an alcoholic, and her steady, almost controlled use of alcohol was very different from my chaotic use of many different kinds of drugs.) I had a very bad attitude, and made my mother's home unsafe to live in. Police would bust the house at least twice a year for about 10 years. People would come to the house demanding money; one time, I was even kidnapped, and my mother had to bail me out. I had my life threatened several times during my drug use, and I used to keep guns, knives, CS gas and a whole range of weapons in my mother's house. My younger brothers suffered as a result of this behaviour, and the only time they ever felt safe was when I was in prison. My mother found me when I almost died from an overdose, and watched me waste away to nothing over years of drug abuse.

I first accessed treatment services when I was 18. I obtained a methadone script, which was eventually three times a week, but I had absolutely no interest in coming off drugs. I used to sell my script most of the time in those days, and viewed my drugs worker as an inconvenience. I didn't need him at that stage, as I wasn't destitute, and was just taking the piss. One month, when I wasn't even dependent on opioids, I had to buy some methadone, because I had a routine urine test coming up, and knew that I had to have some meth in my system. I didn't even take the methadone that I scored; I gave it to someone else, and submitted their urine, which I heated up with a lighter in the toilets of the service. In those days, as far as I was concerned, they either didn't give a shit, or just didn't know the score.

Over the years, I got more tired of using and in real need of help. I went through many different services, prescribers, GPs and counsellors, until I eventually arrived at the stage where I was truly ready to give up drugs. It was around this time, at the age of 25, after 16 years of substance misuse, that I had enough. When I got to this stage, I began to be truthful with the workers with whom I came into contact, with reasonable results, although none of the community-based staff could deliver what I needed. Some of them didn't have the skills, personally or professionally, and just couldn't imagine what it was like for me at that point in my life. I had become so immersed in the lifestyle, and had ingrained habitual behaviour, that any work they attempted to do with me was generally ineffective, because the one important aspect of my addiction which they had no control over was my personal circumstances and my immediate environment.

I decided to enter a detox programme while inside prison in November 2003. To gain entry into the programme, I had to agree to go onto the drug-free wing within

the prison, which was a standard prison wing, exactly the same as the rest of the prison. Also, I had to agree to a regime of regular urine testing. The unit wasn't actually drug free in reality, although there were definitely more prisoners who were not using heroin and other drugs, and perhaps a few more positive attitudes. At the time of making the decision, I was absolutely desperate to be detoxified.

Drugs for the detoxification were administered by the prison healthcare team; the programme consisted of a 3-week buprenorphine reduction programme, with one-to-one support on a regular basis, although not by anyone who was a trained drugs worker or counsellor. The unit itself was run by prison officers, managed by two officers in particular who showed the most interest in drug treatment, although they were by no means specialists. It was as close as one could be to a detox centre within that setting, given that the majority of those accessing it had absolutely no intention of trying to become or remain drug free. In spite of this, I was determined to get something out of it, and took advantage of everything that was on offer, such as complementary therapies like auricular acupuncture, relaxation sessions and one-to-one sessions, which I enjoyed. It was respite for me, in the sense that it was a different atmosphere from the prison wing.

I didn't complete the detox in prison, as I was bailed onto a DTTO. On release from prison, I was offered no follow-up support. I went back to my home town and accessed my local drug services, who seeing the effort I had made not to use upon release, got a script sorted out for me on the day that I saw them. I'd been a client at this place for a number of years, but I had never received treatment as efficient as this, and I made full use of it in a positive way. If I had to pinpoint one aspect of the care that was good, it would be the way that the service, at that particular point in my treatment journey, made an effort to provide me with seamless care. From there, I was taken up by my local DTTO team who took my script over. The prescribing nurse and my keyworker in probation agreed that I should be maintained on buprenorphine for the duration of the 12-month order, to try and maximise my chances of addressing my needs at that time.

I didn't complete the DTTO, because I got sick and tired of it. I had a discussion with my personal probation officer about the possibility of entering residential treatment, as I felt unable to cope with the situation I was in at that time. I went into a residential rehabilitation centre in 2004 in order to address my addiction, as I needed a holistic package of care, which thankfully I received during a 12-month programme. I managed to secure a place at a residential rehab, just 6 months after being bailed from prison. The rehab was a therapeutic community with 36 beds and used cognitive behavioural therapy (CBT) techniques. I went through opioid withdrawal without the assistance of any substitutes, or adjunctive medicine. In the end, it was other people that helped me to get through my withdrawals, not chemicals. My relationship with my keyworker in rehab was one of complete honesty, trust and mutual respect. This person was the catalyst that enabled me to explore the underlying issues that underpinned my substance misuse. They helped me achieve this by being empathic, determined and creative in their practice, as well as effectively coordinating my care with other agencies.

I now lead a very happy and fulfilling life. I have chosen not to drink alcohol or use any illicit substances, nor do I commit crime. I have a family of my own now who have never known me under the influence of drugs or alcohol. I work in the drug

treatment field, as a support worker at a residential rehab. I also teach at a pupil referral unit, and I'm half way through a sociology degree with the Open University. In the next academic year, I'm going to take a place at my local university to embark on a degree in social work. I plan to specialise in working with families with substance misuse problems. I currently sit on an advisory group that informs social work students about transferring their academic skills into good practice.

Although my drug use led to a few physical ailments, I feel relatively healthy now, as I've been drug free for nearly 4 years. When I entered residential rehab, a GP referred me to a liver specialist, who treated the hepatitis, and I've been clear of the virus for nearly 2 years.

I have many tools that aid me in my recovery at present, all of which I've accumulated over time. I believe that every individual has their own unique set of circumstances, thus their own set of precursors or reasons that lead to problematic drug use in the first place. Based on this, I would say that each person needs to find what is right for them, not just in terms of treatment, but also after treatment. Personally, I keep myself extremely busy, not just with my social-care-related work, but in everything I do. I make sensible choices when it comes to who I associate with, where I live (I've subsequently relocated) and how I behave towards others.

3.12 IMPACT OF DRUG MISUSE ON FAMILIES AND CARERS

There is an increasing recognition that drug misuse affects the entire family and the communities in which these families live. The NTA user satisfaction survey found that 25% of respondents felt that staff did not offer families and carers enough support (Best *et al.*, 2006a). The Home Office's updated Drug Strategy (2002) includes targets on increasing access to help, advice and counselling for parents, carers and families of people who misuse drugs. Staff should be particularly aware of the needs of children (ACMD, 2003 & 2007) and consider their own responsibility under the Children Act (1989).

There has also been a growth in carer organisations, most notably Adfam and Families Anonymous, for carers of people who misuse drugs, and over 100 peer-support family groups in the UK founded on parents' own experience of drug use in their families. Families Anonymous is a self-help service based on the 12-steps and is aimed at helping families affected by drug use and behavioural problems (for further details on evidence for the effectiveness of 12-steps and similar approaches, see NCCMH, 2008). Families attend meetings on a regular basis and share their experiences with other families. However, despite the recognition of carers' needs and the growth of carer organisations, there is a rather limited evidence base assessing the impact on carers/families of drug misuse, on interventions intended to support them, and even less attention given to the needs of the family/carer in their own right. Most interventions have targeted carers/families primarily to improve outcomes of the person who misuses drugs and only secondarily to address the needs of the family.

Adfam's report (Sims, 2002) identified a number of needs of families of people who misuse drugs and alcohol. One of the major needs reported by families was

coping with stigma. It was argued that stigma was a major barrier in preventing carers or family members from accessing services, both in terms of actual exclusion from primary care services as well as self-exclusion through fear of being judged. A further need was to access services. Provision of services for families of people who misuse drugs was found to be rather limited (see also Bancroft *et al.*, 2002), but even where these services were available, many families were either not aware of them or did not know how to access them. Many families also perceived themselves to be excluded from participation in the treatment provided for their family member. Some families felt that workers were hiding behind confidentiality when they could have provided general information about treatment. Families may also have different treatment goals from the person misusing drugs and staff involved in his or her care.

The involvement of families and carers remains problematic, but many families express a clear desire for the person with a drug problem to become abstinent and detoxification has a clear role to play in this. Appropriate involvement of family members in the assessment and engagement process may both support the family member and facilitate a more successful outcome. Some psychosocial interventions also explicitly involve family members with the aim of maintaining abstinence following detoxification (see Chapter 7).

3.12.1 Clinical practice recommendations

3.12.1.1 Staff should discuss with people who present for detoxification whether to involve their families and carers in their assessment and treatment plans. However, staff should ensure that the service user's right to confidentiality is respected.

3.12.1.2 Staff should ask families and carers about, and discuss concerns regarding, the impact of drug misuse on themselves and other family members, including children. Staff should also:

- offer family members and carers an assessment of their personal, social and mental health needs
- provide verbal and written information and advice on the impact of drug misuse on service users, families and carers
- provide information about detoxification and the settings in which it may take place
- provide information about self-help and support groups for families and carers.

3.13 ECONOMIC IMPACT OF DRUG MISUSE

Drug misuse is a growing public health concern that carries a substantial economic burden. It is associated with high healthcare and social costs, mainly as a result of transmission of infectious disease, crime and violence (Petry *et al.*, 2004). It has been estimated that problematic drug use accounts for annual social costs in England and Wales

of approximately £11,961 million, or £35,455 per user, per year (Godfrey *et al.*, 2002). Chronic health problems comprise a significant element of the health and social care costs of drug misuse. It has been estimated that the prevalence of HIV among new injecting drug users in London reaches 4.2% (Judd *et al.*, 2005). Godfrey and colleagues (2002) estimated the median number of HIV-positive injectors in England and Wales in 2002 to comprise 931 asymptomatic individuals, 1,756 symptomatic and 1,007 with AIDS. The same authors estimated the median per person annual cost of combination therapy at £13,381 for asymptomatic, £14,222 for symptomatic and £24,314 for people with AIDS. These estimates yielded median annual costs to the NHS of £12.5 million, £25 million and £24 million, respectively, totalling over £60 million.

In 1999, the reported prevalence of hepatitis B in injecting drug users was estimated at 25% among those attending agencies in London and 17% outside London, with a combined estimate for England and Wales of 21% (Godfrey *et al.*, 2002). Based on these estimates, the same study calculated that the number of injecting drug users who were infected with hepatitis B in 2002 was roughly 54,000. An annual cost of £143 per year assumes a lifetime cost of £4,300 to treat people with hepatitis over their average life expectancy of 30 additional years (Godfrey *et al.*, 2002). The annual NHS treatment cost of hepatitis B for injecting drug users was therefore calculated at approximately £7.8 million (Godfrey *et al.*, 2002). Similar estimates for hepatitis C (based on a median 2002 estimate of 81,782 injecting drug users with the virus) yielded an annual NHS treatment cost of £11.7 million (Godfrey *et al.*, 2002). Beyond the healthcare costs incurred directly by the users, the NHS costs relating to treatment of neonates affected by mothers' drug misuse were calculated at £4.3 million per year (Godfrey *et al.*, 2002), with the annual cost of social services in caring for these children amounting to £63 million.

Including primary care, emergency departments, inpatient care, community mental health, and inpatient mental healthcare, problem drug users are estimated to cost the health service between £283 million and £509 million per year (Godfrey *et al.*, 2002). This estimate was in addition to psychosocial interventions, which at present cost £1,000 per user, per year (Godfrey *et al.*, 2002). Furthermore, drug misuse substantially increases crime-ralated costs. Godfrey and colleagues (2002) estimated that the criminal justice system and crime victim costs were £2,366 million and £10,556 million respectively, based on the medium estimates of the number of problematic drug users. Criminal justice costs include costs associated with drug arrests for acquisitive crimes, stays in police custody, appearances in court, and stays in prison; crime victim costs refer to material or physical damage, crime victims' loss and expenditures taken in anticipation of crime.

The above estimates did not consider the impact of current drug use on future healthcare demands, the lost output of the victim or perpetrator of crime, nor the intangible effects on the community at large, such as security expenditure, property depreciation or increased reliance on private transportation. It is therefore evident that drug misuse places a considerable economic burden to the health service and society as a whole.

4. METHODS USED TO DEVELOP THIS GUIDELINE

4.1 OVERVIEW

The development of this guideline drew upon methods outlined by NICE (*The Guidelines Manual*[1] [NICE, 2006a]). A team of healthcare professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the development of a patient-centred, evidence-based guideline. There are six basic steps in the process of developing a guideline:

- Define the scope, which sets the parameters of the guideline and provides a focus and steer for the development work
- Define clinical questions considered important for practitioners and service users
- Develop criteria for evidence searching and search for evidence
- Design validated protocols for systematic review and apply to evidence recovered by search
- Synthesise and (meta-) analyse data retrieved, guided by the clinical questions, and produce evidence profiles
- Answer clinical questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence base for the clinical and cost effectiveness of opioid detoxification for people who misuse drugs. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by good practice points and recommendations agreed by the whole GDG.

4.2 THE SCOPE

Guideline topics are selected by the Department of Health (DH) and the Welsh Assembly Government, which identify the main areas to be covered by the guideline in a specific remit (see *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (second edition)*[2] [NICE, 2006b]). The remit for this guideline was translated into a scope document by staff at the NCCMH (see Appendix 1).

The purpose of the scope was to:

- provide an overview of what the guideline would include and exclude

[1]Available from: www.nice.org.uk
[2]Available from: www.nice.org.uk

- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the National Collaborating Centre and the remit from the DH/Welsh Assembly Government
- inform the development of the clinical questions and search strategy
- inform professionals and the public about the expected content of the guideline
- keep the guideline to a reasonable size to ensure that its development could be carried out within a 12-month period.

The draft scope was subject to consultation with stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from stakeholder organisations and the Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by the GRP.

4.3 THE GUIDELINE DEVELOPMENT GROUP

The GDG consisted of: two service users and a carer, and professionals from psychiatry, clinical psychology, pharmacology, toxicology, nursing, general practice, the prison service and the private and voluntary sectors. The guideline development process was supported by staff from the NCCMH, who undertook the clinical literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

4.3.1 Guideline Development Group meetings

Nine GDG meetings were held between January 2006 and April 2007. During each day-long GDG meeting, in a plenary session, clinical questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflict of interests, and service user and carer concerns were routinely discussed as part of a standing agenda.

4.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Topic group 1 covered questions relating to pharmacology and physical treatments; topic group 2 covered psychosocial treatments; topic group 3 covered inpatient and prison settings; and topic group 4 covered testing methods. These groups were designed to efficiently manage the large volume of evidence appraisal prior to presenting it to the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the healthcare professionals). Topic groups refined the clinical questions and the clinical definitions of treatment interventions, reviewed and prepared the

evidence with the systematic reviewer before presenting it to the GDG as a whole, and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting that section of the guideline relevant to the work of each topic group.

4.3.3 Service users and carers

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included two service users and a carer. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guideline's introduction and identified recommendations from the service user and carer perspective.

4.3.4 Special advisors

Special advisors, who had specific expertise in one or more aspects of treatment and management relevant to the guideline, assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 3 lists those who agreed to act as special advisors.

4.3.5 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the development of the guideline. They informed the group about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment, and trial data if the GDG could be provided with full access to the complete trial report. Appendix 6 lists researchers who were contacted.

4.4 CLINICAL QUESTIONS

Clinical questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. Before the first GDG meeting, draft questions were prepared by NCCMH staff based on the scope and an overview of existing guidelines. They were then discussed by the GDG at their first two

meetings and amended as necessary. Where appropriate, the questions were refined once the evidence had been searched and, where needed, sub-questions were generated. The final list of clinical questions can be found in Appendix 7.

For questions about interventions, the PICO (patient, intervention, comparison and outcome) framework was used. This structured approach divides each question into four components: the patients (the population under study), the interventions (what is being done), the comparisons (other main treatment options) and the outcomes (the measures of how effective the interventions have been) (see Text Box 2).

Text Box 2: Features of a well-formulated question on effectiveness intervention – the PICO guide

Patients/population	Which patients or population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?
Intervention	Which intervention, treatment or approach should be used?
Comparison	What is/are the main alternative/s to compare with the intervention?
Outcome	What is really important for the patient? Which outcomes should be considered: intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning and other measures such as quality of life; general health status; costs?

For questions relating to diagnosis, the PICO framework was not used, since such questions do not involve an intervention designed to treat a particular condition. Rather, the questions were designed to pick up key issues specifically relevant to diagnostic tests, for example their accuracy, reliability, safety and acceptability to the patient.

In some situations the prognosis of a particular condition is of fundamental importance, over and above its general significance in relation to specific interventions. Areas where this is particularly likely to occur relate to assessment of risk, for example in terms of behaviour modification or screening and early intervention. In addition, questions related to issues of service delivery are occasionally specified in the remit from the DH/Welsh Assembly Government. In these cases, appropriate clinical questions were developed to be clear and concise.

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of clinical questions of relevance to NICE guidelines. These are listed in Text Box 3. For each type of question the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

However, in all cases, a well-conducted systematic review of the appropriate type of study is likely to always yield a better answer than a single study.

Deciding on the best design type to answer a specific clinical or public health question does not mean that studies of different design types addressing the same question were discarded.

Text Box 3: Best study design to answer each type of question

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial (RCT); other studies that may be considered in the absence of an RCT are the following: internally/ externally controlled before and after trial, interrupted time-series
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in a randomised trial or inception cohort study
Rates (of disease, patient experience, rare side effects)	Cohort, registry, cross-sectional study
Costs	Naturalistic prospective cost study

4.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible, and if evidence is not available, consensus methods were used (see Section 4.5.6) and the need for future research was specified.

4.5.1 Methodology

A step-wise, hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed this process based on methods set out in the *The Guidelines Manual*[3] (NICE, 2006a) and after considering recommendations from a range of other sources. These included:

- Centre for Clinical Policy and Practice of the New South Wales Health Department
- Clinical Evidence Online
- The Cochrane Collaboration

[3]Available from: www.nice.org.uk

- Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) Working Group
- New Zealand Guideline Group
- NHS Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Oxford Systematic Review Development Programme
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Health Research and Quality.

4.5.2 The review process

After the scope was finalised, a more extensive search for systematic reviews and published guidelines was undertaken. Existing NICE guidelines were updated where necessary. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as appropriate.

At this point, the review team, in conjunction with the GDG, developed a review protocol that detailed all comparisons necessary to answer the clinical questions. The initial approach taken to locating primary-level studies depended on the type of clinical question and availability of evidence.

The GDG decided which questions were best addressed by good practice based on expert opinion, which questions were likely to have a good evidence base and which questions were likely to have little or no directly relevant evidence. Recommendations based on good practice were developed by informal consensus of the GDG. For questions with a good evidence base, the review process depended on the type of key question (see below). For questions that were unlikely to have a good evidence base, a brief descriptive review was initially undertaken by a member of the GDG.

Searches for evidence were updated 6–8 weeks before the stakeholder consultation. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

The search process for questions concerning interventions

For questions related to interventions, the initial evidence base was formed from well-conducted RCTs that addressed at least one of the clinical questions. Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, the RCT remains the most important method for establishing treatment efficacy (this is discussed in more detail in appropriate clinical evidence chapters). For other clinical questions, searches were for the appropriate study design.

All searches were based on the standard mental health related bibliographic databases (EMBASE, MEDLINE, PsycINFO, Cochrane Library, CINAHL) for all trials potentially relevant to the guideline. The search was not restricted to English language publications but included papers from other languages where native speakers were available to translate.

Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 10 for quality criteria

used to assess systematic reviews). However, in some circumstances existing datasets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

After the initial search results were scanned liberally to exclude irrelevant papers, the review team used a purpose-built 'study information' database to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to (a) repeat the search using subject-specific databases (for example, AMED, SIGLE or PILOTS), (b) conduct a new search for lower levels of evidence, or (c) adopt a consensus process (see Section 4.5.6). Future guidelines will be able to update and extend the usable evidence base starting from the evidence collected, synthesised and analysed for this guideline.

In addition, searches were made of the reference lists of all eligible systematic reviews and included studies, as well as the list of evidence submitted by stakeholders. Known experts in the field (see Appendix 6), based both on the references identified in early steps and on advice from GDG members, were sent letters requesting relevant studies that were in the process of being published[4]. In addition, the tables of contents of appropriate journals were periodically checked for relevant studies.

The search process for questions of diagnosis and prognosis

For questions related to diagnosis and prognosis, the search process was the same as described above, except that the initial evidence base was formed from studies with the most appropriate and reliable design to answer the particular question. That is, for questions about diagnosis, the initial search was for cross-sectional studies and for questions about prognosis, it was for cohort studies of representative patients. In situations where it was not possible to identify a substantial body of appropriately designed studies that directly addressed each clinical question, a consensus process was adopted (see Section 4.5.6).

Search filters

Search filters developed by the review team consisted of a combination of subject heading and free-text phrases. Specific filters were developed for the guideline topic, and where necessary, for each clinical question. In addition, the review team used filters developed for systematic reviews, RCTs and other appropriate research designs (see Appendix 8).

Study selection

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. Eligibility criteria were developed for each clinical question and are described in the relevant clinical evidence chapters. Eligible systematic

[4]Unpublished full trial reports were also accepted where sufficient information was available to judge eligibility and quality (see section on unpublished evidence overleaf).

reviews and primary-level studies were critically appraised for methodological quality (see Appendix 10 and Appendix 15 [the characteristics of reviewed studies tables]). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

For some clinical questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the topic groups took into account the following factors when assessing the evidence:

- participant factors (for example, gender, age and ethnicity)
- provider factors (for example, model fidelity, the conditions under which the intervention was performed and the availability of experienced staff to undertake the procedure)
- cultural factors (for example, differences in standard care and differences in the welfare system).

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context and then decide how it should modify its recommendations.

Unpublished evidence

The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline (therefore, the GDG did not accept evidence submitted as commercial in confidence). However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

4.5.3 Data extraction and synthesising the evidence

Outcome data were extracted from all eligible studies that met the quality criteria. Where possible, meta-analysis was used to synthesise the evidence using Review Manager 4.2.8 (Cochrane Collaboration, 2005). If necessary, reanalyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

Where possible, dichotomous efficacy outcomes were calculated on an intention-to-treat basis (that is, a 'once-randomised-always-analyse' basis). This assumes that those participants who ceased to engage in the study – from whatever group – had an unfavourable outcome. Adverse effects were entered into Review Manager as reported by the study authors because it was usually not possible to determine whether early withdrawals had an unfavourable outcome. For the outcome 'leaving the study early for any reason', the denominator was the number randomised.

Included/excluded studies tables, generated automatically from the study information database, were used to summarise general information about each study (see

Appendix 15). Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were also presented in the included studies table (and included, where appropriate, in a narrative review).

Consultation was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer was checked by the second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad *et al.*, 1996; Berlin, 1997).

4.5.4 Presenting the data to the GDG

Summary characteristics tables and, where appropriate, forest plots generated with Review Manager, were presented to the GDG, in order to prepare an evidence profile for each review and to develop recommendations.

Evidence profile tables

An evidence profile table was used to summarise both the quality of the evidence and the results of the evidence synthesis (see Table 1 for an example of an evidence profile table). Each table included details about the quality assessment of each outcome: number of studies, the study design, limitations (based on the quality of individual studies; see Appendix 10 for the quality checklists and Appendix 15 for details about each study), information about the consistency of the evidence (see below for how consistency was measured), directness of the evidence (that is, how closely the outcome measures, interventions and participants match those of interest) and any other considerations (for example, effect sizes with wide confidence intervals [CIs] would be described as imprecise data). Each evidence profile also included a summary of the findings: number of patients included in each group, an estimate of the magnitude of the effect, and quality of the evidence. The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness and any other considerations) and graded using the following definitions:

- **High** = Further research is very unlikely to change our confidence in the estimate of the effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
- **Very low** = Any estimate of effect is very uncertain.

For further information about the process and the rationale of producing an evidence profile table, see GRADE (2004).

Table 1: Example of GRADE evidence profile for buprenorphine versus adrenergic agonists (not all outcomes are shown)

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Buprenorphine**	**Adrenergic agonists**	**Relative (95% CI)**	**Absolute (95% CI)**	**Quality**	**Importance**
Completion of treatment Janiri (1994), Nigam (1993), Raistrick (2005), Lintzeris (2002), O'Connor (1997)											
5	RCT	No limitations	No important inconsistency	No uncertainty	None	196/267 (73.4%)	145/267 (54.3%)	RR 1.33 (1.18 to 1.52)	–	⊕⊕⊕⊕ High	9
Completion of treatment in adolescents Marsch (2005)											
1	RCT	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (−1)[1]	13/18 72.2%	7/18 38.9%	RR 1.86 (0.97 to 3.54)	–	⊕⊕⊕◯ Moderate	9
Completion of withdrawal Janiri (1994), Lintzeris (2002), Nigam (1993), O'Connor (1997)											
4	RCT	No limitations	Important inconsistency (−1)[2]	No uncertainty	None	88/160 55%	68/164 41.5%	RR 1.27 (0.92 to 1.75)	–	⊕⊕⊕◯ Moderate	9

Abstinence for outpatient Ling (2005), Lintzeris (2002)											
2	RCT	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[3]	72/135 53.3%	11/92 12%	RR 3.59 (2.07 to 6.25)	–	⊕⊕⊕⊕ High	9
Abstinence for inpatient Ling (2005)											
1	RCT	No limitations	No important inconsistency	No uncertainty (−1)	Imprecise or sparse data (−1)[1] Strong association (+1)[3]	59/77 76.6%	8/36 22.2%	RR 3.45 (1.85 to 6.43)	–	⊕⊕⊕⊕ Moderate	9
Mean peak withdrawal Lintzeris (2002), Nigam (1993), O'Connor (1997)											
3	RCT	No limitations	No important inconsistency	No uncertainty	None	133	133	–	SMD −0.61 (−0.86 to −0.36)	⊕⊕⊕⊕ High	9

[1]One study
[2]$I^2 > 50\%$
[3]RR > 2

Forest plots

Forest plots were used to present the results of the meta-analyses to the GDG (see Appendix 16). Each forest plot displayed the effect size and CI for each study, as well as the overall summary statistic.

For dichotomous data, the graphs were generally organised so that the display of data in the area to the right of the 'line of no effect' indicated a favourable outcome for the treatment in question. Dichotomous outcomes were presented as relative risks (RRs) with the associated 95% CI (for an example, see Figure 1). A relative risk (or risk ratio) is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control.

The CI shows with 95% certainty the range within which the true treatment effect should lie and can be used to determine statistical significance. If the CI does not cross the 'line of no effect', the effect is statistically significant.

For continuous data, the graphs were generally organised so that the display of data in the area to the left of the 'line of no effect' indicated a favourable outcome for the treatment in question. Continuous outcomes were analysed as weighted mean differences (WMD), or as standardised mean differences (SMD) when different measures were used in different studies to estimate the same underlying effect (for an example, see Figure 2). If provided, intention-to-treat data, using a method such as 'last observation carried forward', were preferred over data from completers.

To check for consistency between studies, both the I^2 test of heterogeneity and a visual inspection of the forest plots were used. The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson, 2002). The I^2 statistic was interpreted in the following way:

- >50%: notable heterogeneity (an attempt was made to explain the variation, for example outliers were removed from the analysis or sub-analyses were conducted to examine the possibility of moderators. If studies with heterogeneous results

Figure 1: Example of a forest plot displaying dichotomous data

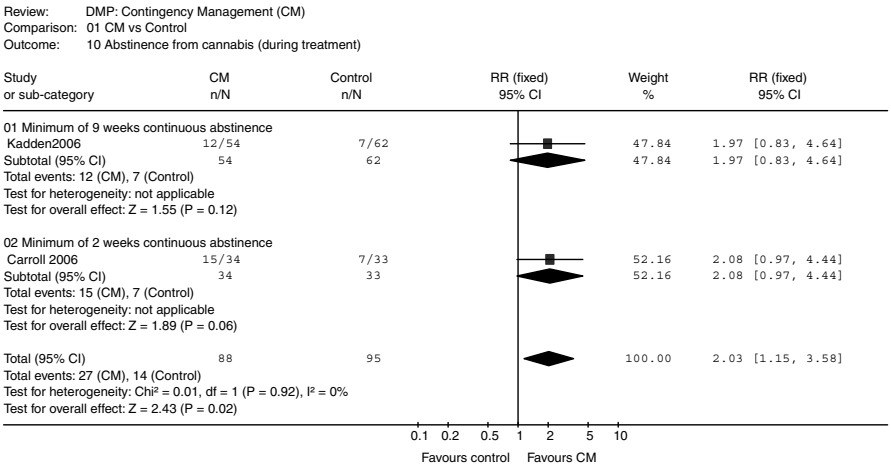
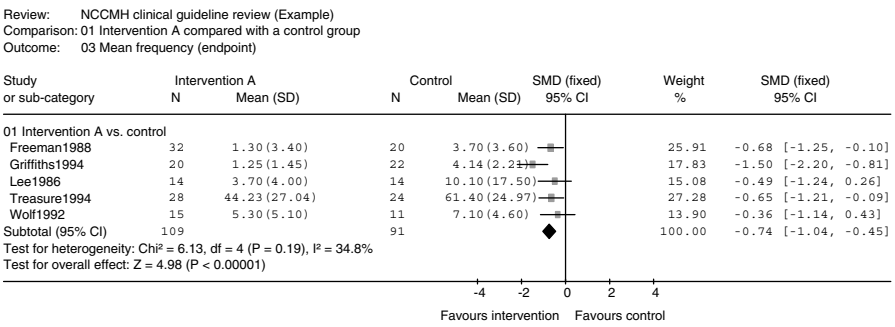


Figure 2: Example of a forest plot displaying continuous data



were found to be comparable, a random-effects model was used to summarise the results (DerSimonian & Laird, 1986). In the random-effects analysis, heterogeneity is accounted for both in the width of CIs and in the estimate of the treatment effect. With decreasing heterogeneity, the random-effects approach moves asymptotically towards a fixed-effects model).

- 30–50%: moderate heterogeneity (both the chi-squared test of heterogeneity and a visual inspection of the forest plot were used to decide between a fixed- and random-effects model).
- <30%: mild heterogeneity (a fixed-effects model was used to synthesise the results).

4.5.5 Forming the clinical summaries and recommendations

The included study tables, forest plots and evidence profiles formed the basis for developing the evidence summaries and recommendations.

For intervention studies, quality assessment was conducted using SIGN methodology (SIGN, 2002) and classified according to a hierarchy (see Text Box 4).

Once the evidence profile tables and evidence summaries were finalised and agreed by the GDG, recommendations were developed, taking into account factors from the evidence, including trade-offs between the benefits and risks of treatment. Other important factors that were considered in developing recommendations included economic considerations, values of the GDG and society, and the group's awareness of practical issues (Eccles *et al.*, 1998).

4.5.6 Consensus method used to answer a key question in the absence of appropriately designed, high-quality research

In the absence of level-1 evidence (or a level that is appropriate to the question), or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there was unlikely to be such evidence, a consensus

Text Box 4: Levels of evidence for intervention studies

Level	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 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 and case series)
4	Expert opinion, consensus methods

*Studies with a level of evidence '–' should not be used as a basis for making a recommendation.
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process was adopted. This process focused on those questions that the GDG considered a priority.

The starting point for the process of consensus was that a member of the topic group identified, with help from the systematic reviewer, a narrative review that most directly addressed the key question. Where this was not possible, a brief review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the clinical question and to lead to written statements for the guideline. The process involved a number of steps:

1. A description of what is known about the issues concerning the clinical question was written by one of the topic group members.
2. Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question.
3. Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the clinical question but were thought to contain relevant data.

4. If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was conducted.
5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question was developed.
6. Following this, on occasions and as deemed appropriate by the GDG, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.
7. Recommendations were then developed and could also be sent for further external peer review.
8. After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

4.6 SYSTEMATIC ECONOMIC LITERATURE REVIEW

The aim of the economic literature review was to contribute to the guideline's development by providing evidence on the relative cost effectiveness of different treatment options covered in the guideline. This process had two stages:

- identification of the areas with likely major cost impacts within the scope of the guideline
- systematic review of existing evidence on the cost effectiveness of different detoxification treatment options for problem drug misuse.

In areas with likely major resource implications where economic evidence did not already exist, economic modelling was undertaken alongside the guideline development process, in order to provide cost-effectiveness evidence and assist decision making.

4.6.1 Key economic issues

The following areas relating to the management of drug misuse were identified by the GDG in collaboration with the health economist as the key issues that should be considered in the guideline:

- cost effectiveness of contingency management in opioid detoxification
- cost effectiveness of various settings for detoxification.

4.6.2 Search strategy

For the systematic review of economic evidence on detoxification for drug misuse the standard mental health related bibliographic databases (EMBASE, MEDLINE, CINAHL and PsycINFO) were searched. For these databases, a health economics search filter adapted from the Centre for Reviews and Dissemination (CRD) at the University of York was used in combination with a general filter for drug misuse. The

subject filter employed a combination of free-text terms and medical subject headings, with subject headings having been exploded. Additional searches were performed in specific health economics databases (NHS EED, OHE HEED), as well as in the HTA database. For the HTA and NHS EED databases, the general filter for drug misuse was used. OHE HEED was searched using a shorter, database-specific strategy. Initial searches were performed in April 2006. The searches were updated regularly, with the final search undertaken between 4 and 6 weeks before the final submission to NICE.

In parallel with searches of electronic databases, reference lists of eligible studies and relevant reviews were searched by hand. Studies included in the clinical evidence review were also screened for economic evidence.

The systematic search for economic evidence on detoxification resulted in 12 potentially relevant studies. Full texts of all potentially eligible studies (including those for which relevance/eligibility was not clear from the abstract) were obtained. These publications were then assessed against a set of standard inclusion criteria by the health economists, and papers eligible for inclusion were subsequently assessed for internal validity. The quality assessment was based on the checklists used by the *British Medical Journal* to assist referees in appraising full and partial economic analyses (Drummond & Jefferson, 1996) (see Appendix 12).

4.6.3 Selection criteria

The following inclusion criteria were applied to select studies identified by the economic searches for further analysis:

- No restriction was placed on language or publication status of the papers.
- Studies published from 1990 onwards were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.
- Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.
- Selection criteria based on types of clinical conditions and patients were identical to the clinical literature review.
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.
- Full economic evaluations that compared two or more options and considered both costs and consequences (that is, cost-minimisation analysis [CMA], cost–consequences analysis [CCA], cost-effectiveness analysis [CEA], cost–utility analysis [CUA] or cost–benefit analysis [CBA]), were included in the review.

4.6.4 Data extraction

Data were extracted by the health economist using a standard economic data extraction form (see Appendix 13).

4.6.5 Presentation of the results

The economic evidence identified by the health economics systematic review is summarised in the respective chapters of the guideline, following presentation of the clinical evidence. The characteristics and results of all economic studies included in the review are provided in the form of evidence tables in Appendix 14. Results of additional economic modelling undertaken alongside the guideline development process are also presented in the relevant chapters.

4.7 STAKEHOLDER CONTRIBUTIONS

Professionals, service users and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- Service user/carer stakeholders: the national service user and carer organisations that represent people whose care is described in this guideline
- Professional stakeholders: the national organisations that represent healthcare professionals who are providing services to service users
- Commercial stakeholders: the companies that manufacture medicines used in the treatment of drug misuse
- Primary Care Trusts
- DH and Welsh Assembly Government.

Stakeholders have been involved in the guideline's development at the following points:

- Commenting on the initial scope of the guideline and attending a briefing meeting held by NICE
- Contributing possible clinical questions and lists of evidence to the GDG
- Commenting on the draft of the guideline.

4.8 VALIDATION OF THIS GUIDELINE

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. The GRP also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE. NICE then formally approved the guideline and issued its guidance to the NHS in England and Wales.

5. ASSESSMENT AND TESTING

5.1 INTRODUCTION

Testing and assessment are important aspects in the management of detoxification. Clinical assessment is important in deciding if detoxification is appropriate for the service user (that is, if he or she is opioid dependent) and, if so, how most effectively to manage the detoxification. Assessment is also important during detoxification, including the careful monitoring of the service user's progress and the level of his or her withdrawal symptoms.

This chapter will discuss the process of conducting a clinical assessment before and during detoxification. Additionally, the use of testing of body fluids and the use of formal psychometric measurement as aids to clinical assessment and treatment/monitoring will be considered.

5.2 CLINICAL ASSESSMENT IN THE MANAGEMENT OF DETOXIFICATION

5.2.1 Clinical assessment of dependence

Most service users presenting for detoxification will show a clear history of opioid dependence, whether by being on prescribed methadone or buprenorphine, or by the clinical presentation of signs of illicit heroin use (for example, abundance of needle marks). Some may have been misusing other opioids additional to any prescribed medication. Often service users may also misuse and be dependent on benzodiazepines and/or alcohol, or stimulants such as cocaine or amphetamines.

It is important that any opioid detoxification regimen should be appropriate to the service user's degree of dependence and the extent of the withdrawal symptoms he or she experiences. Errors have occurred where service users have persuaded the health-care professional conducting a clinical assessment that their degree of opioid use and/or dependence is significantly greater than it is in reality; in some such cases they have had no dependence on or even use of opioid drugs at all. This can lead to the prescription of dangerously high doses of opioids. Adequate assessment of a service user's opioid dependence status is therefore crucial prior to undertaking opioid detoxification.

Opioid dependence is normally diagnosed primarily through a clinical assessment but can be assisted by testing for drugs in biological fluids and by the use of psychometric measures. The clinical assessment of opioid dependence involves asking the service user about the pattern and nature of his or her drug use, the extent of use and treatment episodes in the past, to ascertain the degree of dependence (DH, 1999). A formal psychometric measure may sometimes be employed as an aid to the

assessment of dependence. For example, dependence is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) when three or more of the following criteria are present in a 12-month period: tolerance; withdrawal; increasing use over time; persistent or unsuccessful attempts to reduce use; preoccupation or excessive time spent on use or recovery from use; negative impact on social, occupational or recreational activity; and continued use despite evidence of its causing psychological or physical problems (APA, 1994).

The use of biological testing is important to confirm the reported use of specific drugs, including prescribed and illicit opioids and other non-opioid drugs. In addition, an examination of physical and psychiatric health is important to assist diagnosis of dependence and to assess any further complication to the process, such as comorbid physical or mental health problems or pregnancy (DH, 1999).

The clinical assessment of opioid dependence aids the clinician in determining the level of caution required during detoxification. In particular, if the service user has a low level of dependence or uncertain tolerance, it is vital that detoxification is conducted in a setting that allows the clinician to observe withdrawal symptoms and titrate medication accordingly. In general, detoxification is not required for people who misuse drugs but are not dependent. In addition, caution is also required where polysubstance use or possible polysubstance dependence (commonly alcohol and benzodiazepines) is detected. Polysubstance dependence can complicate the detoxification process and settings for titration therefore need to be appropriate for the level of observation required.

Where a clinical assessment determines that the service user is misusing alcohol, in addition to being opioid dependent, attempts should be made to address this. The possibility should also be noted that a service user may substitute alcohol for his or her previous opioid misuse during or after the detoxification process. Where alcohol dependence is present, detoxification of alcohol should also be considered either before (in community-based settings) or, if there is adequate medical supervision (for example, inpatient settings), concurrently with opioid detoxification.

If a service user is dependent on benzodiazepines, the severity of dependence and the preference of the service user should be taken into account when deciding whether to detoxify from benzodiazepines concurrently or separately from opioids.

5.2.2 Clinical assessment and monitoring of withdrawal

It is important to assess both objective and subjective withdrawal symptoms, at the start of treatment and during the induction and withdrawal stages. This is necessary in order to titrate the medication to alleviate withdrawal symptoms (DH, 1999). The objective signs of withdrawal can be assessed through careful monitoring of the service user's pulse, blood pressure, agitation and sedation. In addition, asking the service user about the subjective signs of distress should also form part of the assessment. Formal psychometric tools may be useful in that they aid standardisation, but they are not a substitute for appropriate clinical assessment. Regular review is

crucial because an overdose of methadone during detoxification may initially present as sedation and/or sleepiness, with under dosing presenting as agitation and anxiety.

5.2.3 Clinical practice recommendations

Clinical assessment of dependence

5.2.3.1 People presenting for opioid detoxification should be assessed to establish the presence and severity of opioid dependence, as well as misuse of and/or dependence on other substances, including alcohol, benzodiazepines and stimulants. As part of the assessment, healthcare professionals should:

- use urinalysis to aid identification of the use of opioids and other substances; consideration may also be given to other near-patient testing methods such as oral fluid and/or breath testing
- clinically assess signs of opioid withdrawal where present (the use of formal rating scales may be considered as an adjunct to, but not a substitute for, clinical assessment)
- take a history of drug and alcohol misuse and any treatment, including previous attempts at detoxification, for these problems
- review current and previous physical and mental health problems, and any treatment for these
- consider the risks of self-harm, loss of opioid tolerance and the misuse of drugs or alcohol as a response to opioid withdrawal symptoms
- consider the person's current social and personal circumstances, including employment and financial status, living arrangements, social support and criminal activity
- consider the impact of drug misuse on family members and any dependants
- develop strategies to reduce the risk of relapse, taking into account the person's support network.

5.2.3.2 For women who are opioid dependent during pregnancy, detoxification should only be undertaken with caution.

5.2.3.3 For people who are opioid dependent and have comorbid physical or mental health problems, these problems should be treated alongside the opioid dependence, in line with relevant NICE guidance where available.

Care for people who misuse other medicines and/or substances in addition to opioids

5.2.3.4 If a person presenting for opioid detoxification also misuses alcohol, healthcare professionals should consider the following.

- If the person is not alcohol dependent, attempts should be made to address their alcohol misuse, because they may increase this as a response to opioid withdrawal symptoms, or substitute alcohol for their previous opioid misuse.

- If the person is alcohol dependent, alcohol detoxification should be offered. This should be carried out before starting opioid detoxification in a community or prison setting, but may be carried out concurrently with opioid detoxification in an inpatient setting or with stabilisation in a community setting.

5.2.3.5 If a person presenting for opioid detoxification is also benzodiazepine dependent, healthcare professionals should consider benzodiazepine detoxification. When deciding whether this should be carried out concurrently with, or separately from, opioid detoxification, healthcare professionals should take into account the person's preference and the severity of dependence for both substances.

5.3 DRUG TESTING

5.3.1 Introduction

The analysis of human body fluids can yield important information in support of healthcare professionals' caring for service users who are about to undertake, or who are undertaking, opioid detoxification. Such analyses are only an adjunct to an appropriate clinical investigation of the service user. Currently, no single test is available that is able to establish or confirm a diagnosis of drug dependence.

In drug misuse services, oral fluid or urine testing are commonly employed, while hair and blood testing are utilised to a lesser extent (NACB, 2006). The numerous testing procedures available can provide evidence of drug consumption, trend of use over time when repeated, and compliance with prescribed drugs.

Moreover, testing may also be useful during a longer-term detoxification, to assess compliance with prescribed medication and to ascertain possible use of illicit drugs. Random intermittent interval testing is probably the most clinically and cost-effective regime. It will help the clinician in confirming the clinical picture and aid assessment of the success of detoxification and possible need to review dosage.

Testing occurs in a variety of settings, including specialist drug services, primary care, residential units, prisons and some hospital settings. The rationale for testing is to help confirm opioid use and to assess other complicating factors, as well as monitoring of care. Testing can be conducted at point of care (that is, near-patient testing) or can be confirmed in a laboratory. Both forms of testing are important tools in clinical practice and will be considered in the sections below.

5.3.2 Near-patient testing

Near-patient testing refers to the process of obtaining a biological sample from a service user and using a drug-testing kit to detect immediately the presence of any of a variety of substances (for example, opioids, amphetamines, cocaine metabolite, benzodiazepines, methadone and cannabis) on site. This process eliminates the need for external laboratory support and provides rapid results.

In current practice, oral swabs or urine screening kits are most commonly used for near-patient testing. These forms of testing are used for a variety of reasons, including monitoring within a criminal justice order, arrest referral schemes, prison systems and medicolegal situations.

Current rapid screening of biological samples for misused drugs depends on immunochemical techniques. Essentially, antibodies with a specific and high affinity for a particular drug, and/or its metabolites, react with the drug present in the sample. The extent to which the antibodies have become bound to drugs present in the sample is then detected by one of several different techniques. All immunochemical methods have problems in relation to specificity, whereby the antibody employed may react with compounds in the sample other than those that the test is intended to measure (DH, in press). There are also potential issues with matrix effects, whereby problems with the sample may destroy the drug/metabolite or the antibody, or interfere with the reaction between the two.

While new technologies based on techniques such as Fourier transform infrared spectroscopy and nanotechnology are under active development and techniques using liquid chromatography in combination with tandem mass spectroscopy are starting to come into use in the laboratory, for the next 2–3 years immunochemical techniques are likely to be the basis of most rapid screening inside the laboratory or at the point of service-user contact.

The analytical, quality and safety issues involved with near-patient testing are well known to clinical laboratories (George & Braithwaite, 2002). For example, false positives may result where the identification of a specific substance may be due to the presence of artefacts or compounds in the biological matrix that are similar to the drug of interest (NACB, 2006). False positive results may also occur due to misinterpretation of a test result. The presence of morphine in urine is often assumed to be indicative of heroin use but may also reflect the consumption of analgesic preparations or poppy seeds (Mule & Casella, 1988).

The problems involved with ensuring results obtained with tests undertaken outside of the laboratory, such as pregnancy or blood glucose testing, are fit for purpose have been well described (George & Braithwaite, 2002). For example, when urine dipsticks are used, colour change must be detected to indicate the presence of an illicit substance; however, this can be difficult for the inexperienced eye (George & Braithwaite, 2002) and such processes are highly subjective. Samples must also be kept in adequate conditions, as they are susceptible to contamination. Some testing kits are only able to determine whether a drug is present but not the type or quantity.

Training and meticulous attention to the manufacturer's instructions are essential for test results to match the levels of performance (for example, sensitivity and specificity) found in validation studies. Further, experience with other analytes measured outside the laboratory suggests the necessity for continued training of staff and the need for the use of quality assurance techniques. Where service users are being assessed in a clinic within a district general hospital, it is arguable that there is no need for near-patient testing of urine samples.

Urinalysis

Urinalysis remains the most reliable tool for identifying drug use in a drug using population (DH, in press). A further advantage of this testing method is that it can detect drug use during the previous few days. Most opioids can be detected between 2 and 3 days after use, methadone up to 9 days and cannabis up to 27 days after use (DH, 1999). However, caution must be exercised when interpreting results of urinalysis as there are a number of products commercially available specifically designed to produce false negative urinalysis results by seeking to remove illicit drugs from the body (NACB, 2006). These substances have the ability to either dilute urine samples or partially eliminate drugs, thereby making detection of illicit drugs difficult.

A recent targeted screening study by Tomaszewski and colleagues (2005) in a US emergency department found promising sensitivity and specificity for near-patient urine testing for opioids (sensitivity = 100%, specificity = 98.7%) and cocaine use (sensitivity = 96.8%, specificity = 100%), but lower sensitivity for cannabis use (sensitivity = 87.5%, specificity = 99.3%) when a comparison was made with confirmatory laboratory tests.

However, lower levels of sensitivity and specificity have been reported elsewhere. This is illustrated by the experience of the prison service, where urine samples for mandatory drug testing are collected under a high degree of supervision. On average, of all samples submitted where a screening test had produced a positive result, the confirmation test, using definitive analytical procedures such as gas chromatography/mass spectroscopy, or liquid chromatography/mass spectroscopy, did not confirm the positive screening test on 11% of occasions (HM Prison Service, 2005). In the case of opioids, only 90% of positive tests on screening were confirmed to be positive by definitive testing; for benzodiazepines this was 70%, for methadone 80% and for amphetamines 50% (HM Prison Service, 2005). It should be noted that screening tests on samples submitted for mandatory testing in prison are carried out in the laboratory using sophisticated analytical equipment rather than with kits at the point of contact.

Oral fluid testing

The major advantages of oral fluid drug testing are that it can potentially be relatively easily obtained and is less intrusive than urinalysis. It is also less open to adulteration. These properties enable oral fluid testing to be conducted by personnel with relatively little training, while maintaining an acceptable balance between service-user dignity and sample integrity (DH, in press). On the other hand, many opioid users will have a dry mouth on presentation for detoxification and may have genuine difficulty in providing a suitable sample. A further problem of oral fluid testing is that the detection time of drug use is considerably shorter than for urinalysis, generally providing information on use within the last 24 hours (DH, in press; Verstraete, 2004). Drug concentration can also differ depending on the collection method. Stimulation of saliva flow is often used. This can be problematic because the pH for stimulated flow is approximately 8, compared with the basal saliva pH of 6.5. Therefore any drug with a pKa around these values will be substantially affected and may lead to decreased drug concentration (NACB, 2006).

Thirdly, there is a lack of evidence on interferences, oral drug residues, and other issues of manipulation that may affect the validity of this matrix (NACB, 2006).

There is limited evidence for the sensitivity and specificity of oral fluid testing products (DH, in press). In a small study (N = 15), results obtained by law enforcement officers correlated well with laboratory results for cocaine and amphetamines but were unsatisfactory for detecting heroin and cannabis use (Samyn & van Haeren, 2000). Gronholm and Lillsunde (2001) also found poor sensitivity for detecting benzodiazepines and cannabinoids for oral fluid testing.

5.3.3 Confirmation of screening tests

Confirmatory tests are often needed to reduce false positive results; this may relate to adulteration of the sample or a false interpretation when medications that are chemically similar to the drug of interest are taken legitimately. Conversely, a negative test may not rule out dependence. This may be due to a number of factors, such as the sample being taken some time after drug ingestion, adulteration of the sample or threshold of sensitivity of the analytical procedure in the laboratory.

Confirmation of screening test results is a sophisticated laboratory exercise that requires a considerable investment in skilled staff and dedicated equipment. In general, it is not a service that can be set up or completed rapidly with non-specialised staff or equipment.

The majority of the cases presenting for detoxification will involve opioids detectable by near-patient testing. However, some opioids, including buprenorphine, fentanyl, oxycodone, pethidine and others, are not detectable under standard immunochemical tests and would produce a false negative near-patient test result. If there is uncertainty after a clinical assessment about the drug use or dependence of a service user, confirmatory laboratory testing should be considered.

Confirmatory laboratory testing should be capable of detecting service users who deliberately contaminate their urine with heroin or methadone in order to produce a false positive result. Heroin use may be ascertained in the laboratory by the demonstration of compounds such as 6-monoacetylmorphine, codeine, acetylcodeine, meconin and possible others in urine. There is also a need to confirm the presence of both methadone and its principal metabolite in urine.

The standard of testing in a laboratory providing screening and/or confirmatory services should be high, with appropriately trained staff who all participate in programmes of continuing professional education. There should be appropriate established standard operating and safety procedures in place, and participation in quality assurance schemes that assess not just the analytical capabilities of the laboratory but also the ability of the laboratory staff to interpret results.

In order for a laboratory to react appropriately to an analytical request, the sample must be unequivocally identified and appropriate clinical information must be provided. The format of the report should be clear and should be accompanied by sufficient information to enable the report to be interpreted by the person responsible for the management of the service user's care. For example, if a report indicates the

presence of 6-monoacetylmorphine, then the significance of this should be explained in text below the analytical result; that is, that this metabolite is unique to heroin and can distinguish between the use of codeine prescriptions or poppy seed consumption (which may result in a morphine positive urine sample) and heroin use (Mule & Casella, 1988). The nature of the substance identified should be described accurately and unambiguously; for instance, it would be inappropriate for a near-patient testing instrument that identifies the presence of opioids to report a sample as being positive for heroin.

Where the laboratory is remote from the treatment facility, arrangements must be in place for the rapid and secure electronic reporting of results. Both the laboratory and the care providers should have protocols in place to ensure that results are reported rapidly by the laboratory and reviewed quickly and efficiently by the care providers.

5.3.4 Summary

Testing of biological fluids for misused drugs is an important tool to ensure safety in the care of service users undergoing opioid detoxification. At present, most data on testing is for urinalysis and this remains the most reliable tool for clinical practice. Screening of biological fluids for the presence of opioid drugs should be carried out by techniques that are fit for purpose by adequately trained staff who continue to maintain their skills. Ease of collection, training implications and the equipment required also need to be taken into consideration.

However, the interpretation of tests for the presence of drugs and their metabolites cannot be divorced from knowledge of the clinical circumstances and the donation of the sample. The clinician must also have knowledge of the characteristics of the tests, their limitations and the interpretation of a variety of tests in different settings. If there is uncertainty about the service user's drug dependence, the clinician may wish to defer initiation of detoxification until confirmatory tests are available. If initiating with only screening tests, the clinician must be certain of clinical dependence or organise detoxification in a setting with adequate observation and dose titration.

Training is important for all clinicians, who should have the support of appropriate and trained laboratory staff. Protocols should be available regarding the practical aspects of taking tests, their refrigeration if appropriate, the need for supervised samples, the extent to which service users should be supervised while providing a sample (that is, the frequency and intrusiveness of the supervision), the need for confirmatory testing and ensuring clinical governance and quality assurance of this aspect of care.

Urinalysis is the most reliable tool for identifying drug use and has higher sensitivity and specificity than oral fluid testing for a number of substances (DH, in press). In addition, urinalysis is substantially less costly than oral fluid testing. Therefore, the routine use of urinalysis is more cost effective, since it represents a more efficient use of limited NHS resources. Healthcare professionals should normally consider using urinalysis for drug testing as the first choice, and consider oral fluid testing only in circumstances were urinalysis is impractical or unacceptable to the service user.

5.3.5 Clinical practice recommendations

5.3.5.1 If opioid dependence or tolerance is uncertain, healthcare professionals should, in addition to near-patient testing, use confirmatory laboratory tests. This is particularly important when:

- a young person first presents for opioid detoxification
- a near-patient test result is inconsistent with clinical assessment
- complex patterns of drug misuse are suspected.

5.3.5.2 Near-patient and confirmatory testing should be conducted by appropriately trained healthcare professionals in accordance with established standard operating and safety procedures.

5.3.5.3 Healthcare professionals should be aware that medications used in opioid detoxification are open to risks of misuse and diversion in all settings (including prisons), and should consider:

- monitoring of medication concordance
- methods of limiting the risk of diversion where necessary, including supervised consumption.

5.4 PSYCHOMETRIC ASSESSMENT TOOLS

5.4.1 Introduction

The importance of a clinical assessment of opioid (and other drug or alcohol) dependence and monitoring withdrawal before and during detoxification has been discussed above (see Section 5.2). This section is concerned with the use of psychometric instruments as adjuncts to clinical assessment and monitoring.

Crome and colleagues (2006) argue that there are a number of advantages for the use of assessment tools. Recording is standardised, and a checklist of domains ensures that important issues are covered and that multidisciplinary professionals have a common understanding of what has been assessed. Furthermore, the implementation of tools over time can be utilised to demonstrate progress to the service user and to measure outcome. Finally, the use of assessment tools is empirically testable and therefore it is possible to evaluate the reliability and validity of these tools. The reliability and validity of the psychometric tools used to assess dependence and monitor withdrawal are discussed below.

5.4.2 Assessment of dependence

Identification (simple assessment) tools have most recently been reviewed by NICE (2007; National Collaborating Centre for Mental Health, 2008). The present review will focus on assessment of dependence.

There have been a number of recent reviews evaluating assessment tools for drug misuse (Crome *et al.*, 2006; Scottish Executive, 2003; Sperling *et al.*, 2003). Crome and colleagues (2006) and the Scottish Executive (2003) briefly evaluated the

assessment tools. Sperling and colleagues (2003) conducted a more detailed consensus-based evaluation of these measures on training/costs, administration, UK relevance, psychometric properties and content, providing an overall summary percentage score of the extent to which these criteria were judged to be fulfilled.

Self-report questionnaires

The Leeds Dependence Questionnaire (LDQ; Raistrick *et al.*, 1994) is a ten-item self-report scale designed to measure dependence on a variety of substances, to be sensitive to change over time (although follow-up data in validation was not long enough to assess this) and to account for the range of mild to severe dependence. Concurrent validity was assessed by comparing the LDQ with the Severity of Opiate Dependence Questionnaire (SODQ) for opioid users and a moderate association was found ($r = 0.30$). Additionally, there was a high level of internal consistency (Cronbach $\alpha = 0.94$). Sperling and colleagues' (2003) consensus-based evaluation of this measure rated it very highly (97%).

The Severity of Dependence Scale (SDS; Gossop *et al.*, 1995) is a short (five-item) self-report scale designed to measure the degree of dependence on a variety of drugs. The SDS is related to behavioural patterns of drug taking such as heroin dose ($r = 0.24$), frequency of heroin use ($r = 0.43$) and duration of use ($r = 0.27$). In addition, it has good concurrent validity, with treatment-seeking participants reporting higher mean scores ($t = 10.00$, $p < 0.001$) than non-treatment seeking controls (Gossop *et al.*, 1995). The scale was also found to have a high level of internal consistency (Cronbach α ranging from 0.84 to 0.90 in heroin-user samples). There are mixed reviews of the utility of this measure for clinical practice. Sperling and colleagues (2003), on the same criteria listed above (training/costs, administration, UK relevance, psychometric properties and content), rated this measure the most highly (99%) of all the assessment scales they reviewed. However, another reviewer expressed major concerns about the use of this scale as a measure of dependence due to the lack of items on tolerance and withdrawal (Scottish Executive, 2003).

Clinician-administered questionnaires

The Addiction Severity Index (ASI; McLellan *et al.*, 1980) is a clinician-administered multi-dimensional 200-item measure with seven main areas: medical, employment/support, alcohol, drug, legal, family/social and psychiatric. This assessment tool has been investigated extensively. Makela (2004), in a review of 37 studies on the psychometric properties of the ASI, concluded that there were inconsistent findings on inter-rater reliability, test-retest reliability, and internal consistency for this scale. Furthermore, this scale was not rated very highly (69%) in a review of assessment scales, mainly due to difficulties administering such a large measure in clinical practice, training costs and relevance to the UK (Sperling *et al.*, 2003).

The Opiate Treatment Index (OTI; Darke *et al.*, 1992) is a clinician-administered multi-dimensional measure with sub-scales on drug use, HIV risk behaviour, social functioning, criminality, health and psychological adjustment. Test–retest reliability correlations were large and ranged from 0.88 to 0.96. Associations between the OTI and the ASI generally ranged from $r = 0.43$ to $r = 0.70$; however, the correlation

between the criminality subscale and the legal subscale of the ASI was very low ($r = 0.02$). Additionally, agreement between self-report and collateral report (partner or family member) was relatively high. Sperling and colleagues (2003) did not rate this measure particularly highly (73%), citing problems with relevance to the UK and difficulties with administration in clinical practice.

The Maudsley Addiction Profile (MAP; Marsden *et al.*, 1998) is a clinician-administered 60-item scale covering the following domains: substance use, health risk, physical/psychological health and personal/social functioning. Concurrent validity was acceptable, with high correlations ($r = 0.72$) between the physical and psychological health measure and items adapted from the ASI. Similarly, for the relationship conflict measures of the MAP there were high correlations ($r = 0.74$) with subscales from the Life Stress and Social Resources Inventory (LISRES). In addition, there was high test–retest reliability averaging 0.94 overall and 0.88 for reported substance use. This measure was also rated highly (96%) by Sperling and colleagues (2003). However, the reviews of both Sperling and colleagues (2003) and the Scottish Executive (2003) advised caution concerning the length of the scale and therefore the ease of administration in clinical practice. As a response to such criticisms, the MAP has recently been adapted into a shorter (20-item) self-completion version (Luty *et al.*, 2006). There were relatively large correlations ($r = 0.70$) between the adapted self-completion and the original interviewer-completion version of the MAP.

The Christo Inventory for Substance-Misuse Services (CISS; Christo *et al.*, 2000) is a ten-item clinician-administered measure including social functioning, general health, sexual/injecting risk behaviour, psychological functioning, occupation, criminal involvement, drug/alcohol use, ongoing support, compliance and working relationships. Relatively large correlations were found with the OTI (generally ranging from $r = 0.70$ to 0.91). There was also good inter-rater reliability with Pearson's correlations of $r = 0.84$ and an intraclass correlation of 0.82 (Christo *et al.*, 2000). The reviews of both Sperling and colleagues (2003) and the Scottish Executive (2003) suggested problems with the content of this measure, suggesting it may be too simplistic.

5.4.3 Monitoring of withdrawal

The most important aspects of monitoring objective and subjective withdrawal symptoms in clinical practice are to determine that over- or under-prescribing is not occurring and that the service user is comfortable on his or her dose. This is primarily monitored by clinical assessment, but the use of psychometric measures can aid this process.

Scales measuring withdrawal are commonly categorised as objective (clinician-rated) or subjective (self-report). There are several scales that have been developed to monitor the withdrawal process; these include: the Clinical Opiate Withdrawal Scale (COWS; Wesson & Ling, 2003), Opiate Withdrawal Scale (OWS; Bradley *et al.*, 1987), Short Opiate Withdrawal Scale (Gossop, 1990) and the Subjective and Objective Withdrawal Scales (Handelsman *et al.*, 1987).

The self-reported OWS was assessed during a 20-day detoxification trial of 84 participants (Bradley *et al.*, 1987). The pattern of withdrawal as measured by the scale was as expected. As methadone dose was reduced, a rise in distress was reported that faded by the end of the third week to a total withdrawal score in the normal range (derived from a non-dependent control group). There was a relatively small correlation ($r = 0.25$) between the self-report OWS and nurse observation of withdrawal, although correlations between nurse observation and the OWS were much higher when the nurse-observed rating was high ($r = 0.71$). Gossop (1990) compared the Short Opiate Withdrawal Scale (10 items) with the OWS (32 items). A very high correlation ($r = 0.97$) was found between these measures, suggesting the usefulness of the shorter version.

The Subjective and Objective Opiate Withdrawal Scales were assessed for 32 participants admitted for inpatient detoxification (Handelsman *et al.*, 1987). Significant changes were found for both scales at the stabilisation stage of the trial and after a naloxone challenge.

The COWS is a clinician-rated measure. There appears to be little validation of this measure, with the exception that all items have been validated in previous measures (Wesson & Ling, 2003).

5.4.4 Summary

The development of psychometric tools to assess dependence and monitor withdrawal is still at an early stage. Although data were relatively sparse for most measures, some had reasonable reliability and validity. The use of reliable and valid assessment tools may aid the process of conducting a clinical assessment and monitoring withdrawal during the process of detoxification.

6. PHARMACOLOGICAL AND PHYSICAL INTERVENTIONS IN OPIOID DETOXIFICATION

6.1 INTRODUCTION

The aim of detoxification for a dependent opioid user is to eliminate the effects of opioid drugs in a safe and effective manner (WHO, 2006). Appropriate administration of pharmacological agents plays a crucial role in increasing the likelihood of a successful detoxification, while minimising the discomfort of withdrawal experienced by the service user.

6.1.1 The psychopharmacology of opioid dependence

This section sets out the key aspects of the pharmacology of the opioids and other drugs used in detoxification, including the use of opioid agonists, partial agonists and opioid antagonists. In addition, the pharmacology of tolerance and withdrawal will be briefly discussed within the context of detoxification and the use of opioid and non-opioid drugs (for example, alpha$_2$ adrenergic agonists) to manage withdrawal symptoms.

Opioid agonists
All opioids, including heroin and methadone, are agonists that stimulate opioid receptors. Many opioid agonists are also prescribed for their analgesic properties in pain management, including morphine, codeine, dihydrocodeine, oxycodone, hydrocodone and fentanyl.

Partial agonists
Buprenorphine is a partial agonist at the μ opioid receptor subtype, which means that the system is not fully stimulated even when all the receptors are occupied. This lesser effect is the main contributory mechanism underlying buprenorphine's better safety profile when taken alone, since the threshold for respiratory depression is not reached even when all the receptors are occupied (Walsh *et al.*, 1994).

As a partial agonist, buprenorphine can also appear to act as an antagonist (and as such may have been described in older literature as a mixed agonist-antagonist). If buprenorphine is given to a person who has taken a full agonist (for example, heroin or methadone), it displaces the full agonist, due to buprenorphine's higher affinity at the μ opioid receptor, but only partially stimulates these receptors. The difference in activation results in the individual experiencing withdrawal. This can be seen when

people convert from their street drug or high-dose methadone to buprenorphine. Therefore a partial agonist behaves like an agonist in the presence of no other agonist; in the presence of high levels of an opioid agonist, it behaves like an antagonist.

Buprenorphine is also an antagonist at the κ receptor and therefore may be less likely to lower mood compared with an agonist.

Tramadol is a more complex drug; its pharmacology is currently not well understood, but it could either be a low-potency μ agonist or a partial agonist. It is more commonly used in the context of pain relief.

Antagonists

An antagonist, such as naltrexone or naloxone, binds to the receptor but does not stimulate it. Naltrexone and naloxone have a high affinity with opioid receptors, such that they will displace existing agonists and prevent further agonists from binding to the receptors. Therefore if an agonist is present stimulating the receptor, for example heroin or methadone, taking naltrexone or naloxone will stop this stimulation, resulting in precipitated (abrupt) withdrawal. For these reasons, naloxone is commonly used in emergency medicine to reverse opioid overdose, while the longer acting naltrexone is prescribed as a maintenance treatment to prevent detoxified service users from relapsing to opioid use.

Tolerance

If opioids are taken repeatedly, their effects are diminished due to the development of tolerance. This means that, in order to achieve the same effect, more of the drug has to be taken. Depending on the effect, tolerance can occur at different rates; for instance, tolerance to euphoria occurs much faster than tolerance to respiratory depression.

Such pharmacological tolerance to opioids is not clearly defined in the literature, but it is likely that it involves changes in opioid receptor availability and function through changes within the cell or effects on other neurotransmitter systems, for example noradrenaline (Maldonado, 1997). In a dependent opioid user, changes in the brain's circuitry (involving reward, learning and impulse control) also occur. The brain's opioid system is thought to play a significant role in mediating reward to other drugs of misuse including alcohol and cocaine (Herz, 1997; Van Ree *et al.*, 2000). Tolerance can also vary depending on the context or environment in which the opioid is being taken and can lead to a dose of opioids producing more or less of an effect than expected (Siegel *et al.*, 1982).

Withdrawal

When a person who has become tolerant to the effects of a drug stops taking it, withdrawal symptoms ensue. These may vary in their intensity depending on the level of opioid use as well as other factors such as context and environment. Minimising these symptoms, which emerge within 6–12 hours from short-acting opioids such as heroin and about 24–36 hours after the last dose of methadone or buprenorphine, depending on the dose, is the main aim in any opioid detoxification programme. Although previously divided into psychological and physical symptoms, such a distinction has limited clinical utility given that physical withdrawal can have a large psychological component. Withdrawal can also ensue when an opioid antagonist, such as naloxone

or naltrexone is taken; this is called precipitated or abrupt withdrawal. While the withdrawal syndrome for opioids is rarely life-threatening (unlike that for alcohol, due to the potential for seizures and delirium tremens), the discomfort for some people makes it hard to withstand.

Opioid withdrawal consists of a constellation of symptoms, such as pupil dilation, diarrhoea, low mood, irritability, anxiety, insomnia, muscular and abdominal pains, restlessness and 'craving'. In addition, tachycardia, sweating, runny nose, hair standing on end, shivering, goosebumps (hence the term 'going cold turkey') are generally experienced. The latter symptoms are known to be associated with hyperactivity of the noradrenaline system (called a 'noradrenergic storm') that occurs to compensate for tolerance at the opioid receptor. This provides the rationale and clinical efficacy for using medication that reduces noradrenergic activity, such as lofexidine or clonidine (alpha$_2$ adrenergic agonists).

The contribution of changes in the opioid system directly producing withdrawal symptoms is less clear, although increased receptor availability has been shown (Williams, 2007). Gradual reductions of opioid medication should result in the complete absence of, or minimal, withdrawal symptoms. However, medication acting on the noradrenergic system will only ameliorate particular symptoms (see above), necessitating use of other medications to manage all withdrawal symptoms.

The role of the GABA-benzodiazepine receptor is also not certain, but opioids taken over long periods can alter this system (Sivam *et al.*, 1982; Rocha *et al.*, 1993), which may be the basis on which benzodiazepines (such as diazepam and temazepam) are often prescribed during detoxification or used by dependent opioid users when they cannot obtain heroin.

6.2 PHARMACOLOGICAL INTERVENTIONS IN DETOXIFICATION

6.2.1 Introduction

This section reviews the evidence for pharmacological interventions in detoxification for opioid dependent adults and young people. For the purposes of this guideline, a young person is defined as an individual aged 16–18, and studies have been included for review only if they were judged to include a significant proportion of participants aged 16 or above (that is in each given study, at least 50% of participants are aged 16 years or over; where such information is not provided, mean age is greater than or equal to 15.5 years).

Opioid agonists and partial agonists

The most straightforward pharmacological approach to detoxify a dependent opioid user is by reducing over a period the dose of an opioid substitute medication, for example methadone or buprenorphine. As described above, this should cover all the symptoms of withdrawal. Depending on the substitute medication and starting dose, detoxification can take days to months. For methadone, the most rapid regimes last 7–21 days, while 'slow tapering' regimens can last up to 6 months or longer (DH, 1999). Detoxification with

buprenorphine is usually faster than with methadone, and can in theory be completed within less than a week, though 14 days to several weeks appears to be typical.

Although it is pharmacologically possible to detoxify directly via tapered doses of heroin (indeed any opioid agonist), this is rarely recommended clinically because the short elimination half-life of heroin results in a particularly acute and intense withdrawal syndrome. Illicit heroin users are normally first stabilised on an opioid substitute prior to starting detoxification.

Opioid antagonists

Opioid antagonists such as naltrexone and naloxone may be used to speed up the process of detoxification. The aim is to flood the brain with an opioid antagonist to remove all agonists and fully occupy the opioid receptors. If given at the start of detoxification, this will lead to abrupt withdrawal for a dependent user with opioids in his or her system, which can be subjectively extremely unpleasant, depending on the amount of agonist present. Sedation or general anaesthesia are likely to be used here, alongside a variety of adjunctive medications, to minimise discomfort. The service user is then generally maintained on naltrexone to prevent relapse. Use of opioid antagonists in this way is often referred to as ultra-rapid or rapid detoxification and is covered in detail in Section 6.5.

Alternatively, to minimise discomfort, naloxone or naltrexone is started after a few days of detoxification and not at full dose, thus shortening and speeding up detoxification while avoiding the requirement for sedation or general anaesthesia. This approach is covered in greater detail also in Section 6.5.

Adjunctive medications

Adjunctive medications are used to ameliorate symptoms of opioid withdrawal, and the term covers a wide number of medications and uses. Those that target the noradrenaline system, including clonidine and lofexidine, alter a brain system known to be involved in mediating a cluster of opioid withdrawal symptoms and signs. Other forms of adjunctive medications are directed at a specific symptom, such as an antispasmodic for gut cramps, or a collection of symptoms, for instance benzodiazepines for anxiolysis and sedation or antipsychotics for agitation or sedation.

Adjunctive medications are often used during detoxification. Their use is particularly important when conducting a detoxification with non-opioid drugs, such as clonidine or lofexidine, since they are not able to cover all withdrawal symptoms. However, the use of adjunctive medications for symptoms, such as for sedation, is also not uncommon during a detoxification using opioid medications (for example, methadone or buprenorphine).

Therefore it is critical when comparing detoxification regimens in the trials reviewed below that the use of adjunctive medication is taken into consideration. This is especially important when comparing opioids (methadone or buprenorphine) with alpha$_2$ adrenergic agonists (clonidine or lofexidine).

The use of opioid antagonists in addition to other medications is not considered here as a form of adjunctive medication since they do not ameliorate symptoms of withdrawal, although their use can shorten or accelerate detoxification (see above).

Current practice
In the UK, only methadone and buprenorphine are licensed as substitute opioids for the management of opioid dependence. In addition, lofexidine is licensed for symptomatic relief during opioid detoxification. These medications are currently used in the vast majority of opioid detoxifications in the UK. A minority of detoxifications within specialist drug services have involved medications unlicensed for detoxification, including clonidine, naltrexone and dihydrocodeine (Day *et al.*, 2005). Dihydrocodeine has also been used in some primary care and criminal justice settings for opioid detoxification (Wright *et al.*, 2007a).

There appears to be widespread administration of adjunctive medications, most notably benzodiazepines, alongside a 'core' medication for the management of opioid withdrawal symptoms, but a review of UK practice has not been conducted to assess how such adjunctive medication is being prescribed.

In addition, there are a number of service users who have attempted unassisted detoxification (Gossop *et al.*, 1991; Noble *et al.*, 2002; Scherbaum *et al.*, 2005; Ison *et al.,* 2006). This is discussed in more detail in Chapter 8.

6.2.2 Treatment outcomes

Abstinence
This refers to evidence for the absence of opioid use at a particular time point (for example, at the end of treatment or at 3-month follow-up). Measures based on urinalysis or other forms of chemical testing were preferred, but self-report measures were not excluded. However, outcomes relating to abstinence, in particular at follow-up, were not widely reported in the trials identified by the evidence search. Although in the majority of studies abstinence was clearly the important long-term goal of detoxification, in some detoxification resulted in the participant being re-established on substitute medication.

Completion of treatment
This is regarded as an important proxy measure of detoxification success. Completion has typically been defined as being retained in treatment up to the final day of its planned duration, ingestion of the final dose of study medication, or reaching the point of zero dose of study medication.

6.2.3 Side effects and adverse events

During detoxification or withdrawal from opioids, many signs and symptoms can become evident. These can be categorised broadly as due to opioid withdrawal itself or to side effects of the medication given for the detoxification regimen. During the latter stages of detoxification and in early abstinence, some signs and symptoms such as anxiety or insomnia might be the emergence of the person's 'natural state'. For

example, a service user's opioid use may have reduced his or her levels of anxiety or insomnia, but such symptoms may re-emerge during detoxification. In addition to these, adverse events can also occur as a consequence of the medication prescribed and include events predictable from a drug's pharmacology; these can be undesirable and dangerous. It is possible that any symptom or sign could be due to any one or more of these reasons. The considerable heterogeneity among the studies in how withdrawal symptoms, side effects or adverse events were described and attributed makes this difficult to comment on.

Adverse events

Adverse events are a potentially serious consequence of detoxification and may result in significant negative impact on the individual's well-being or in the individual being removed from a study (with some requiring medical attention). Significant concerns have been raised over serious adverse events, including death, especially in relation to rapid and ultra-rapid detoxification, and the sedation and anaesthesia procedures involved (Strang *et al.*, 1997a).

Respiratory depression

The following applies to whenever methadone and buprenorphine are being prescribed rather than particularly referring to the process of detoxification.

As a full μ opioid agonist, methadone can result in respiratory depression. Therefore initiation should be undertaken with care (NICE, 2006c). However, some degree of tolerance to its respiratory depressive effects occurs after a period of methadone use. By contrast, buprenorphine, as a partial agonist at the μ opioid receptor, is not associated with significant respiratory depression when taken at therapeutic doses. During detoxification and in early abstinence, it is presumed that any tolerance to respiratory depression is lost, leading to the warning about potential for 'overdose' and death from respiratory depression.

However, it is important to remember that for both methadone and buprenorphine, interactions with other respiratory depressants such as alcohol, benzodiazepines and the newer non-benzodiazepine hypnotics (Z-drugs), other sedatives or tricyclic antidepressants may also induce serious respiratory depression (NICE, 2006c). The additive or synergistic effects of such depressant drugs, particularly alcohol or benzodiazepines, may play a contributory role in deaths involving either methadone, buprenorphine or other opioid agonists (White & Irvine, 1999; Corkery *et al.*, 2004; Pirnay *et al.*, 2004). Warning individuals about 'potential for overdose' should extend to include concurrent use of respiratory depressant drugs.

Severity of withdrawal

This was generally not reported comprehensively; that is, data were rarely presented for each day over the entire duration of detoxification. The most frequently used scales were the Subjective Opiate Withdrawal Scale and Short Opiate Withdrawal Scale. There was sparse reporting of more protracted withdrawal symptoms that may persist after completion of detoxification. In this analysis, withdrawal scores are

presented as: peak (mean maximum score), lowest (mean minimum score), overall (total or mean score over the duration of detoxification) and mean change from baseline (the difference between mean overall score and mean score at baseline). Subjective rather than objective measures of withdrawal were used, as the former were judged by the GDG as more representative of service-user acceptability. In addition, while it is clearly important to use such validated withdrawal scales in trials, the GDG felt that in routine clinical practice these scales should not replace good clinical skills or knowledge, but that consideration could be given to using them to complement good clinical assessment.

6.2.4 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/exclusion criteria used for this section of the guideline can be found in Table 2.

Table 2: Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological interventions

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005 to January 2007
Study design	RCT
Patient population	Adults and young people who are opioid dependent
Interventions	Methadone, buprenorphine, other opioid agonists, alpha$_2$ adrenergic agonists, opioid antagonists, sedatives (including benzodiazepines and Z-drugs)
Outcomes	Abstinence, treatment completion, safety/adverse events, severity of withdrawal

6.2.5 Studies considered[5]

The review team conducted a new systematic search for RCTs that assessed the efficacy and safety of pharmacological detoxification. In addition, a further search

[5]Here, and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

for observational studies was undertaken to assess the safety of pharmacological detoxification.

The following treatments were included in the review:

- methadone
- buprenorphine
- dihydrocodeine
- clonidine
- lofexidine
- naltrexone
- naloxone
- benzodiazepines
- carbamazepine.

In contrast to other sections of the guideline there are not specific clinical summaries for each drug as most trials compare active treatments with one another rather than placebo or minimal control groups. Therefore an overall summary (see section 6.3) is provided instead that discusses the evidence for effectiveness of the main classes of drugs in comparison with each other, which reflects how these trials were conducted.

6.2.6 Opioid agonists

Methadone

For comparisons of methadone against other opioid agonists, clonidine or lofexidine, 12 RCTs (BEARN1996; GERRA2000; HOWELLS2002; JIANG1993; KLEBER1985; SALEHI2006; SAN1990; SORENSEN1982; TENNANT1975; TENNANT1978; UMBRICHT2003; WASHTON1980) met the eligibility criteria, providing data on 712 participants. All studies were published in peer-reviewed journals (see Table 3 and Table 4 for further details on study information, critical outcomes and overall quality of evidence). The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Comparisons of methadone against buprenorphine are reviewed separately in the section on buprenorphine below.

Table 4 and Table 5 show studies comparing methadone with an $alpha_2$ adrenergic agonist. It was found that methadone had a better adverse–event profile, especially in relation to hypotension (versus clonidine), and that it was associated with better completion of detoxification (versus lofexidine). Where described in these trials, additional adjunct medications were typically not used in either treatment arm (clonidine/lofexidine or methadone).

Methadone did not differ in efficacy compared with other opioid agonists (propoxyphene napsylate, levo-alpha acetylmethadol [LAAM], tramadol). These are neither licensed nor routinely used in the UK for the treatment of opioid dependence.

Table 3: Study information table for trials of methadone for opioid detoxification

	Methadone versus other opioid agonists (LAAM, propoxyphene, tramadol)	**Methadone versus clonidine**	**Methadone versus lofexidine**
Total no. of trials (total no. of of participants)	4 RCTs (N = 192)	6 RCTs (N = 566)	2 RCTs (N = 154)
Study ID	LAAM: SORENSEN1982 Propoxyphene: TENNANT1975 TENNANT1978 Tramadol: SALEHI2006	GERRA2000 JIANG1993 KLEBER1985 SAN1990 UMBRICHT2003 WASHTON1980	BEARN1996 HOWELLS2002
Diagnosis	Opioid dependence	Opioid dependence	Opioid dependence Polydrug use: illicit benzodiazepines 67.6%, crack cocaine 35.2%, cocaine powder 22.1% (HOWELLS2002); benzodiazepines 43% (BEARN1996)

Mean years of opioid use	7.8–9.1 (TENNANT 1975), 13.6–16 (TENNANT1978)	2–6 (GERRA2000)	Heroin: 10.5 (BEARN1996), 8.8–9.5 (HOWELLS2002)
Mean daily opioid use	Not reported	Street heroin: 1.5–2.0 g (GERRA2000)	Heroin: 0.46 g (BEARN 1996)
Treatment length	14 days: SALEHI2006 21 days: SORENSEN1982, TENNANT1975 42 days: TENNANT1978	4 days: UMBRICHT2003 10 days: WASHTON1980 12 days: SAN1990 30 days: KLEBER1985	10 days: HOWELLS2002 20 days: BEARN1996
Length of follow-up	Up to 18 months	None	None
Age	28–37 years	24–40 years	31–32 years

Table 4: Summary evidence table for trials of methadone for opioid detoxification

	Methadone versus other opioid agonists (LAAM, propoxyphene, tramadol)	Methadone versus clonidine	Methadone versus lofexidine
Total no. of trials (total no. of participants)	4 RCTs (N = 192)	6 RCTs (N = 566)	2 RCTs (N = 154)
Study ID	LAAM: SORENSEN1982 Propoxyphene: TENNANT1975 TENNANT1978 Tramadol: SALEHI2006	GERRA2000 JIANG1993 KLEBER1985 SAN1990 UMBRICHT2003 WASHTON1980	BEARN1996 HOWELLS2002
Evidence profile table number (Appendix 17)	Table A17-2	Table A17-1	Table A17-3
Overall quality of evidence	Moderate	Moderate	Moderate
Benefits			
Abstinence	*Endpoint*: 28% versus 31%, RR 0.91 (0.44 to 1.87) K = 1, N = 72 *1-month follow-up*: 11% versus 17%, RR 0.54 (0.02 to 14.86) K = 2, N = 86 *6-month follow-up*: 8% versus 20%, RR 0.42 (0.04 to 3.95) K = 1, N = 22	*During treatment*: 52% versus 42%, RR 1.25 (0.68 to 2.29) K = 1, N = 49 *Endpoint*: 39% versus 38%, RR 1.04 (0.58 to 1.85) K = 2, N = 75 *1-month follow-up*: 32% versus 25%, RR 1.28 (0.52 to 3.14) K = 1, N = 49	—

		3-month follow-up: 32% versus 25%, RR 1.28 (0.52 to 3.14) K = 1, N = 49 *6-month follow-up*: 36% versus 17%, RR 2.16 (0.77 to 6.09) K = 2, N = 71	
Completion of treatment	65% versus 47%, RR 1.44 (0.86 to 2.41) K = 4, N = 192	67% versus 51%, RR 1.20 (0.70 to 2.07) K = 4, N = 287	78% versus 64%, RR 1.22 (0.99 to 1.51) K = 2, N = 154
Started naltrexone maintenance	—	RR 0.50 (0.26 to 0.95) K = 1, N = 66	—
Self-rated withdrawal severity	—	*Peak*: SMD −0.65 (−1.22 to −0.08) K = 1, N = 50 *Change from baseline*: SMD 0.25 (−0.40 to 0.91) K = 1, N = 36	*Peak*: SMD −0.09 (−0.58 to 0.41) K = 1, N = 63 *Lowest*: SMD −0.03 (−0.53 to 0.47) K = 1, N = 63 *Overall*: SMD −0.12 (−0.62 to 0.37) K = 1, N = 63
Harms			
Adverse events	—	*Side effects rating*: SMD −0.92 (−1.18 to −0.66) K = 2, N = 250	*Incidence of hypotension*: RR 0.67 (0.16 to 2.76) K = 1, N = 68

For abstinence, completion and initiation of naltrexone: RR > 1 favours methadone or high-dose methadone. For adverse events, RR < 1 favours methadone. For withdrawal severity, negative SMD favours methadone.

Table 5: Adjunct medications, symptoms and adverse events for opioid detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Methadone versus other opioid agonists (RCTs)			
SALEHI2006	**Methadone** versus **tramadol**	Both groups given 0.3 mg/day clonidine and 10–30 mg/day oxazepam.	Used Short Opiate Withdrawal Scale. Severity of medication side effects evaluated by direct questioning about somnolence, sweating, dizziness, nausea, vomiting and constipation – no difference between the groups at the end of the active medication period, but the methadone group had significantly more drowsiness and sweating at the end of the placebo period. Comment: Listed 'side effects' could be due to withdrawal as opposed to medication.
SORENSEN1982	**Methadone** versus **LAAM**	Not mentioned.	Withdrawal symptom discomfort index combining the frequency and severity of 16 specific symptoms – not listed. One near-lethal overdose in LAAM group in a 26-year-old man who had used heroin and drank heavily during the week. Remained comatose for 3 days, recovered and discharged by 6th day. Urine and blood samples confirmed only opioid metabolites. 'We do not know if this was a toxic response to some unknown adulterant, an idiosyncratic response to methadyl acetate itself, or a combined narcotic and alcohol overdose.'

TENNANT1975	**Methadone** (24 mg) versus **propoxyphene napsylate** (800 mg)	Not mentioned.	Withdrawal and 16 side effects (including constipation, delirium, dysphoria, euphoria, hallucinations, sedation and seizures) were assessed using two separate Himmelsbach scales. At least a few patients in both groups reported every side effect except hallucination and seizures; significantly more propoxyphene patients (47.2%) reported euphoria compared with methadone patients (16.7%).
TENNANT1978	**Methadone** (15 mg) versus **methadone** (25 mg) + **propoxyphene napsylate** (600 mg)	Not mentioned.	Many side effects listed, including numbness and light-headedness. No description of AEs.
Methadone versus clonidine (RCTs)			
GERRA2000	**Clonidine** versus **clonidine with naloxone and naltrexone** versus **methadone**	Clonidine with naloxone and naltrexone group: oxazepam 60 mg twice daily for 2 days, baclofen 10 mg three times daily, ketoprofene IV 400 mg daily. Did not report administration of adjuncts to remaining groups.	Clonidine-only group: showed no withdrawal symptoms apart from insomnia and slight anxiety. Clonidine-naltrexone group: on naltrexone administration, showed some withdrawal symptoms of moderate intensity (tremor, anxiety, tachycardia) that disappeared after a few hours of clonidine IV. Methadone group: presented anxiety, tachycardia, insomnia, rhinorrhoea, mydriasis, aching muscles and irritability. Also showed a consistent level of dysphoria.

Continued

Table 5: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
JIANG1993	**Clonidine** versus **methadone**	Not mentioned.	List of 21 symptoms, including: lethargy, loss of strength, dizziness, dry mouth, fatigue, nausea, drowsiness, lack of balance, discomfort after eating, headache, bloating, tinnitus, unclear vision, itchiness, heartburn, excessive saliva, skin rashes and temperature, pulse, breathing and blood pressure changes. Comment: AEs for clonidine were significantly greater than for methadone, most frequently: dry mouth, then lethargy and dizziness when standing, and also constipation and hypotension, general loss of bodily strength, weakness when walking.
KLEBER1985	**Methadone** (20 mg) versus **clonidine** (0.3 up to 1 mg, depending on withdrawal severity and effect on blood pressure)	The only additional medication permitted during the study was chloral hydrate (0.5–1 g), for insomnia. However: 'A "blind" physician… gave recommendations as to the need for ancillary medication *such as* [emphasis added] for	Withdrawal symptoms assessed by 'blind' nurses and participants on two scales. Side effects assessed by 'blind' physicians and nurses. No description of what items these consisted of. Leaving study early: ten methadone and seven clonidine due to 'rated as experiencing unacceptably high withdrawal symptoms'; one methadone and seven clonidine due to 'rated as experiencing unacceptable side effects'. Side effects in two cases (both clonidine) were severe: one persistent vomiting, one complained of impaired

		sleep… An "open" physician… determined the dose of medication to be used that day as well as any other ancillary medication'. 63% of clonidine group and 70% of methadone group required sleep medications.	breathing and 'throat swelling'. Comment: Hypotension was not a prominent side effect.
SAN1990	**Clonidine** (max 1.05 mg) versus **guanfacine** (max 3.58 mg) versus **methadone** (max 37.3 mg)	'Exceptionally prescribed benzodiazepines'.	'More frequently observed side effects during detoxification' were: Methadone group: hot flashes, asthenia, salivation, mental clouding, thirst Clonidine and guanfacine groups: asthenia, dry mouth, flushing, mental clouding (in that order, and clonidine > guanfacine) Recorded hypotension with clonidine and guanfacine Comment: No description of AEs.
UMBRICHT2003	**Buprenorphine** versus **clonidine** versus **methadone** All participants were HIV positive	Used morphine to control withdrawal symptoms while waiting for enrolment, and also for pain relief during detoxification – data only	Clonidine group: two patients experienced hypotension. Comment: Morphine was likely related to their medical illness (HIV positive) rather than detoxification *per se*, but would expect to have some impact on withdrawal.

Continued

Table 5: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
		available for 53 patients, and 50% had morphine.	
WASHTON1980	**Methadone** versus **clonidine** Dosage regimens individualised	Not mentioned.	'Major withdrawal complaints were nearly identical for the two groups and consisted mainly of lethargy, restlessness, and insomnia.' Clonidine group reported withdrawal symptoms early in study, whereas methadone group reported late (as dose approached zero). Clonidine participants reported sedation, dry mouth, occasional transitory episodes of light-headedness or dizziness upon standing. Comment: Additional symptoms reported by clonidine group were presumably side effects due to medication.
Methadone versus lofexidine (RCTs)			
BEARN1996	**Lofexidine** versus **methadone** (~60 mg)	If on benzodiazepines given some diazepam, otherwise not mentioned.	Two patients (female) experienced dizziness, so lofexidine dose reduced.

HOWELLS2002	**Lofexidine** (0.6 up to 2 mg, then tapered to 0) versus **methadone** (30 mg)	'Only a very small amount' – 4/32 (12.5%) in lofexidine group and 7/36 (19.4%) in methadone group: Two in each group received diazepam for entire duration of study for their benzodiazepine dependence. One in each group taking medication for pre-existing conditions (epilepsy and hereditary angioedema). Two in lofexidine group received medication for insomnia, one in methadone group for nausea and vomiting.	Few occurrences of transient hypotension (sitting systolic blood pressure <90 mmHg) in each group: 12.7% lofexidine, 8.0% methadone. No apparent relationship to dosing. 'No evidence that these… gave rise to clinical concern'. One minor AE in each group (depressive symptoms). No severe or serious AEs reported. Comment: No adverse symptoms reported from 21 participants who left study early (primarily for prison sentence management reasons).

Buprenorphine

For comparisons of buprenorphine with methadone, clonidine or lofexidine, 12 RCTs (CHESKIN1994; JANIRI1994; JOHNSON1992; LING2005; LINTZERIS2002; MARSCH2005; NIGAM1993; O'CONNOR1997; PETITJEAN2002; RAISTRICK2005; SEIFERT2002; UMBRICHT2003) met the eligibility criteria, providing data on 653 participants. While the sublingual preparation of buprenorphine was most commonly used, one study (LING2005) used the buprenorphine-naloxone preparation, and in one study all participants received carbamazepine in both the buprenorphine and methadone groups (SEIFERT2002). Most of the included studies were of adults but one study was of adolescents (MARSCH2005). In addition, one cluster-randomised trial (PONIZOVSKY2006) compared buprenorphine with methadone; this study was not included in the meta-analysis. All were published in peer-reviewed journals, with additional unpublished data for one trial provided by the authors (RAISTRICK2005). For further details on study information, critical outcomes and overall quality of evidence see Table 6, Table 7 and Table 8. The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Comparisons of buprenorphine with dihydrocodeine are reviewed separately in the section on dihydrocodeine below.

All individual RCTs were included in the meta-analyses (see Table 7). People who underwent buprenorphine detoxification achieved clearly better outcomes on most measures, including completion, abstinence and withdrawal severity, compared with those who used clonidine or lofexidine. Buprenorphine did not differ significantly from methadone on completion rate for detoxification; however, no extractable data were available for abstinence outcomes.

Ponizovsky and colleagues' (2006) cluster-randomised trial was not included in the meta-analysis and is thus summarised here. Opioid-dependent participants were randomised to receive a 10-day inpatient detoxification using either buprenorphine (n = 100) or clonidine (n = 100) depending on which hospital they attended. The clonidine protocol also included the use of adjunctive medications as indicated (promethazine, dipyrone, trazodone, phenobarbital and antiemetics). Some 90% of the buprenorphine group completed detoxification, compared with only 50% in the clonidine group, a significant difference (RR = 1.80, 95% CI: 1.46 to 2.21). Abstinence outcomes were not reported. This result was consistent with the other buprenorphine trials meta-analysed above.

Dihydrocodeine

Dihydrocodeine is an opioid agonist licensed in the UK for pain relief. It has also been used in a range of UK settings as a substitute medication for opioid dependence both in maintenance and detoxification (Day *et al.*, 2005; Strang *et al.*, 2005; Wright *et al.*, 2007a, b).

Two RCTs (WRIGHT2007A; SHEARD2007B) comparing dihydrocodeine with buprenorphine met the eligibility criteria, providing data on 150 participants. Protocols for both studies were published in peer-reviewed journals, with unpublished data for both trials provided by the authors (see Table 9 and Table 10 for further details on study information, critical outcomes and overall quality of evidence). The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 6: Study information table for trials of buprenorphine for opioid detoxification

	Buprenorphine versus methadone	Buprenorphine versus clonidine	Buprenorphine versus lofexidine
Total no. of trials (total no. of participants)	4 RCTs (N = 212)	8 RCTs, 1 cluster-randomised trial (N = 631)	1 RCT (N = 210)
Study ID	JOHNSON1992 PETITJEAN2002 SEIFERT2002 UMBRICHT2003	CHESKIN1994 JANIRI1994 LING2005 LINTZERIS2002 MARSCH2005 NIGAM1993 O'CONNOR1997 PONIZOVSKY2006 UMBRICHT2003	RAISTRICK2005
Diagnosis	Opioid dependence Other substance dependence: 33–42% (cocaine; PETITJEAN2002) Other substance misuse: alcohol (50%), cocaine (46%), benzodiazepines (62%) (SEIFERT2002)	Opioid dependence Other substance dependence: alcohol 5.2–12%, cocaine 17.3–22.1%, benzodiazepines 0.9–4.4% (LING2005), alcohol 17–18%, cocaine 3–17%, cannabis 12–22% (MARSCH2005)	Opioid dependence Other substance misuse: 37%, including cannabis (16%), cocaine (15%), benzodiazepines (6%) and alcohol (6%)
Mean years of opioid use	Months of present dependence: buprenorphine 19.8 (14.0), methadone	10.7–12.6 (CHESKIN1994), 7–9 (LING2005), 7.5 (3.6) (JANIRI1994),	

Continued

Table 6: (*Continued*)

	Buprenorphine versus methadone	**Buprenorphine versus clonidine**	**Buprenorphine versus lofexidine**
	38.1 (49.4) to 40.9 (55.9) (JOHNSON1992) Years of opioid misuse: 8.6 (6.8)–10.5 (7.5) (SEIFERT2002), 4.6–4.7 (PETITJEAN2002)	4–5 (NIGAM1993), 7.7–8.9 (O'CONNOR1997)	
Mean daily opioid use	$/day heroin: buprenorphine 114.1 (91.7), methadone 106.2 (49.9) to 115.3 (65.3) (JOHNSON1992)	Frequency of injecting/day: 3.69 (2.09) (LINTZERIS 2002) Other substance use: weekly cocaine 0.38–0.96 g, weekly alcohol 3.3–6.2 drinks (O'CONNOR1997)	£/day heroin: 22–24
Treatment length	4 days: UMBRICHT2003 14 days: SEIFERT2002 16 days: PETITJEAN2002 60 days: JOHNSON1992	4 days: UMBRICHT2003 8 days: LINTZERIS2002, O'CONNOR1997 9 days: JANIRI1994 10 days: NIGAM1993 13 days: LING2005 18 days: CHESKIN1994 28 days: MARSCH2005	7 days (buprenorphine) versus 4 days (lofexidine)
Length of follow-up	None	Up to 1 month	1 month
Age	32–40 years	17 years: MARSCH2005 21–45 years: all other studies	28 years

Table 7: Summary evidence table for trials of buprenorphine for opioid detoxification

	Buprenorphine versus methadone	Buprenorphine versus clonidine	Buprenorphine versus lofexidine
Total no. of trials (total no. of participants)	4 RCTs (N = 212)	8 RCTs (N = 631)	1 RCT (N = 210)
Study ID	JOHNSON1992 PETITJEAN2002 SEIFERT2002 UMBRICHT2003	CHESKIN1994 JANIRI1994 LING2005 LINTZERIS2002 MARSCH2005 NIGAM1993 O'CONNOR1997 UMBRICHT2003	RAISTRICK2005
Evidence profile table number (Appendix 17)	Table A17-6	Table A17-4	Table A17-5
Overall quality of evidence	Moderate	High	Moderate
Benefits			
Abstinence	—	*Maintained throughout treatment*: 22% versus 5%, RR 4.18 (1.26 to 13.90). K = 1, N = 114	*1-month follow-up*: 35% versus 25%, RR 1.37 (0.90 to 2.09) K = 1, N = 210

Continued

Table 7: (*Continued*)

	Buprenorphine versus methadone	Buprenorphine versus clonidine	Buprenorphine versus lofexidine
		Endpoint: 40% versus 8%, RR 4.11 (2.50 to 6.74) K = 3, N = 458 *Maintained for 4 weeks post-treatment*: 9% versus 2%, RR 4.83 (0.58 to 40.03) K = 1, N = 114	
Drug use	*Relapsed during treatment*: 7% versus 17%, RR 0.43 (0.04 to 4.16) K = 1, N = 26	*Days of use at 1-month follow-up:* SMD −0.61 (−1.03 to −0.19) K = 1, N = 91	—
Completion of treatment	44% versus 30%, RR 1.10 (0.82 to 1.48) K = 4, N = 212	74% versus 56%, RR 1.32 (1.15 to 1.52) K = 7, N = 427	65% versus 39%, RR 1.43 (1.11 to 1.84) K = 1, N = 210
Started naltrexone maintenance	—	RR 11.00 (1.58 to 76.55) K = 1, N = 36	—

Self-rated withdrawal severity	*Change from baseline*: SMD −0.44 (−1.08 to −0.20) K = 1, N = 39	*Peak*: SMD −0.51 (−0.77 to −0.25) K = 3, N = 238 *Lowest*: SMD −0.52 (−0.90 to −0.14) K = 2, N = 117 *Overall*: SMD −0.63 (−0.79 to −0.46) K = 6, N = 646 *Change from baseline:* SMD −0.04 (−0.50 to 0.42) K = 2, N = 73	*Peak*: SMD −0.18 (−0.45 to 0.10) K = 1, N = 208 *Lowest*: SMD −0.46 (−0.74 to −0.19) K = 1, N = 208 *Overall*: SMD −0.50 (−0.78 to −0.23) K = 1, N = 208 *Change from baseline*: SMD −0.11 (−0.38 to 0.17) K = 1, N = 203
Harms			
Adverse events	—	*Left study early due to adverse events:* RR 0.19 (0.03 to 1.03) K = 3, N = 106	—

For abstinence, completion and initiation of naltrexone, RR > 1 favours buprenorphine. For relapse and adverse events, RR < 1 favours buprenorphine. For withdrawal, negative SMD favours buprenorphine.

Table 8: Adjunct medications, symptoms and adverse events for buprenorphine detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Buprenorphine versus methadone (RCTs)			
JOHNSON 1992	**Buprenorphine** versus **methadone**	Not mentioned.	None for detoxification – stated: Significant differences were observed between groups on 5 of 14 measures (decreased appetite, difficulty urinating, anxiety, sedation or drowsiness, constipation) – but said that these occurred on maintenance phase, and that there was no pattern of results suggesting any consistent effects either between treatment or across time. Comment: Study concentrates on detoxification after period of maintenance – AEs described appear linked to maintenance and not detoxification.
PETITJEAN 2002	**Buprenorphine** versus **methadone** Dosages according to initial self-reported heroin use, and reduced by clinical judgement	Not mentioned.	Short Opiate Withdrawal Scale and monitoring of 'vital signs.' No mention of adverse events.
SEIFERT2002	**Buprenorphine with carbamazepine** versus **methadone with carbamazepine**	All participants received carbamazepine (200 up to 900 mg).	'No severe side effects occurred during treatment in either group.'

UMBRICHT 2003			See Table 5 [methadone]
Buprenorphine versus clonidine (RCTs)			
CHESKIN1994	**Buprenorphine** versus **clonidine**	Additional medications were available for specific symptoms (for example, diarrhoea) but were not requested nor prescribed.	One clonidine participant left study due to uncontrolled hypertension [sic]. For first 3 days, mean peak and area-under-curve diastolic and systolic blood pressure were significantly lower in clonidine group; returned to baseline within 1 day of medication discontinuation.
JANIRI1994	**Buprenorphine** versus **clonidine**	Not mentioned.	27-item withdrawal scale (with objective, subjective and psychological items) rated by 'blind' psychiatrist, in addition to other signs and symptoms. Reported statistic for each measure. No signs and symptoms not included in the rating scale (including medication side effects) were reported. No significant differences in blood pressure and heart rate.
LING2005	**Buprenorphine-naloxone** versus **clonidine**	Use of ancillary medication was the same in inpatient study for buprenorphine-naloxone and clonidine. Mean ~ 2.7 doses. Also no difference for completers.	Inpatient group – mean number of reported AEs per participant per day was significantly different: buprenorphine-naloxone = 1.5, clonidine = 2.4. No difference in completers. Outpatient group – mean number of reported AEs per participant per day was significantly different: buprenorphine-naloxone = 0.7, clonidine = 1.2. Significant difference in completers: 0.6 versus 1.1.

Continued

Table 8: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
		Outpatient group – also no difference, but in completers only: clonidine group used more medications (3.2 versus 1.7 for buprenorphine-naloxone). 'A range': oxazepam, lorazepam, phenobarbital and hydroxyzine (anxiety and restlessness), ibuprofen, acetaminophen, methocarbamol (bone pain, arthralgia), trimethobenzamide (nausea), loperamide, donnatal (diarrhoea), zolpidem, trazodone, doxepin, diphenhydramine (insomnia). One type of medication per day for one disorder.	Serious AEs: Inpatient – two deaths: respiratory failure in buprenorphine-naloxone, bacterial endocarditis in clonidine group. Neither was due to study medication. In addition: buprenorphine-naloxone – two had suicidal behaviour, one had severe vomiting. Clonidine: vomiting, road traffic accident, cellulitis. Outpatient sites: 14 cases in buprenorphine-naloxone (ten continued substance misuse/overdose, two depression, one severe vomiting, spine surgery?), four in clonidine group (one of each of following: substance misuse, nausea/vomiting, pneumonia, kidney stones). No deaths. Comment: No description of timeframe of AEs.

LINTZERIS 2002	**Buprenorphine** (10 mg) versus **clonidine** (0.9 mg) in dependent heroin users (had not been undergoing methadone maintenance treatment [MMT])	Clonidine group: metoclopramide (mean 17.7 mg, frequency unknown), diazepam (14 mg) or equivalent dose of temazepam, quinine (380 mg), hyoscine (34 mg), ibuprofen (940 mg). Does not appear that buprenorphine group were offered any adjuncts.	Similar reports in both groups. Buprenorphine group: one patient had precipitated withdrawal when given buprenorphine, therefore given diazepam and clonidine. Comments: Outpatient setting with reported illicit heroin use during detoxification, making data difficult to interpret. Presents table of AEs and claims to exclude those attributed to withdrawal or those unrelated to medications or condition being treated – then lists 'precipitated withdrawal, drowsiness, lethargy…'
MARSCH2005	**Buprenorphine** versus **clonidine** Adolescent sample (mean age = 17 years)	All participants offered adjunct over-the-counter medications (such as ibuprofen and sleep aids) as needed to manage symptoms. Number of participants who received these medications, timing, amount and type of use not reported. Existing medications at intake or during study	Self-report rating scale of withdrawal effects (irritability, chills/gooseflesh, runny nose, yawning) and opioid effects (such as nodding, rush, high, coasting, itchy skin). Comment: No mention of adverse events.

Continued

Table 8: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
		were tracked to ensure they were not contraindicated with study medications.	
O'CONNOR 1997	**Buprenorphine** versus **clonidine** versus **clonidine with naltrexone**	Clonidine was prescribed to *all* groups, 0.1–0.2 mg every 4 hours as needed, to control withdrawal symptoms. Following adjunct medications also available to all participants as needed: oxazepam (for insomnia and cramps), ibuprofen or ketorolac (muscle cramps), prochlorperazine (nausea). Number of participants, timing, type and amount taken not reported.	Withdrawal symptoms: 24-item subjective scale. Comment: No mention of adverse events.

NIGAM1993	**Buprenorphine** versus **clonidine**	75% of either group required nitrazepam (15 mg nocte). Aspirin and imodium also given to a 'few'.	Clonidine: greater hypotension (three patients left study as a result); also complaints of giddiness, dry mouth, constipation.
PONIZOVSKY 2006 (cluster-randomised trial)	**Buprenorphine** (median 10 mg) versus **clonidine** (0.15 mg × 4)	Clonidine group: promethazine (150 mg/day), dipyrone (1,500 mg/day), trazodone (100 mg/nocte), phenobarbital (200 mg/nocte), antiemetics. Does not appear that buprenorphine group received these medications.	Significantly lower level of side effects for buprenorphine compared with clonidine. No mention of hypotension. Comment: Does discuss overlap between withdrawal symptoms and side effects.
UMBRICHT 2003	See Table 5 [methadone]		
Buprenorphine versus lofexidine (RCTs)			
RAISTRICK 2005	**Buprenorphine** versus **lofexidine**	Buprenorphine group: vast majority received no adjuncts; however, five participants received chlordiazepoxide on	'No major adverse reactions were reported'. Authors' comments: 'I have checked through the data file and no adverse events at all have been recorded. … A few people had withdrawal precipitated by buprenorphine but this would not

Continued

Table 8: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
		day 1 or day 2. Lofexidine group: published lofexidine protocol began with 1,600 mg on day 1, 'allowed for clinical judgement but in practice the regimens were rarely subject to significant variation'. Majority of participants began with lofexidine (800 mg) and chlordiazepoxide (70 mg). Cophrenotrope, hyoscine butylbromide or chlorpromazine listed in published lofexidine regimen, but appear not to have been used by any participant in either group.	have been logged as an adverse event, rather misjudged [detoxification] management.'

Table 9: Study information and summary evidence table for trials of dihydrocodeine for opioid detoxification

	Buprenorphine versus dihydrocodeine
Total no. of trials (total no. of participants)	2 RCTs (N = 150)
Study ID	WRIGHT2007A SHEARD2007
Diagnosis	Opioid dependence
Mean years of opioid use	7.8 (WRIGHT2007A), 9.3 (SHEARD2007)
Mean daily opioid use	Illicit opioids: £15.60–£23.20 (WRIGHT2007A), £41.05– £45.56 (SHEARD2007)
Treatment length	12 days (dihydrocodeine) versus 9 days (buprenorphine)
Length of follow-up	6 months
Mean age	29–31 years
Evidence profile table number (Appendix 17)	Table A17-7
Overall quality of evidence	Moderate
Benefits	
Abstinence	*Endpoint*: 43% versus 23%, RR 1.90 (1.21 to 3.01) K = 2, N = 150 *1-month follow-up*: 38% versus 35%, RR 1.08 (0.63 to 1.85) K = 1, N = 90 *3-month follow-up*: 33% versus 20%, RR 1.64 (0.94 to 2.86) K = 2, N = 150 *6-month follow-up*: 17% versus 10%, RR 1.71 (0.74 to 3.96) K = 2, N = 150
Completion of treatment	59% versus 46%, RR 1.27 (0.97 to 1.66) K = 2, N = 150

RR > 1 favours buprenorphine.

Table 10: Adjunct medications, symptoms and adverse events for dihydrocodeine detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
Buprenorphine versus dihydrocodeine (RCTs)			
WRIGHT 2007A	**Buprenorphine** versus **dihydrocodeine** Dosages at the discretion of prescribing doctor but within standard regimens	None reported.	No serious adverse events were reported.
SHEARD 2007	**Buprenorphine** versus **dihydrocodeine** Dosages at the discretion of prescribing doctor but within standard regimens	None reported.	No serious adverse events were reported.

People undergoing dihydrocodeine detoxification were less likely to be abstinent at the end of treatment, and appeared to be no more likely to complete detoxification, than those receiving buprenorphine. There is little justification to recommend the routine use of dihydrocodeine in detoxification.

6.2.7 Alpha$_2$ adrenergic agonists

Alpha$_2$ adrenergic agonists (such as clonidine and lofexidine) act to reduce the noradrenergic hyperactivity seen in opioid withdrawal. They are therefore a type of adjunctive medication. They can be either used alone or alongside a rapid reduction in opioid dose; however, this generally requires use of other adjunctive medications to ameliorate those symptoms not associated with noradrenergic hyperactivity. This should be considered and taken into account when comparing regimens.

For comparisons of lofexidine versus clonidine, four RCTs (CARNWATH1998; GERRA2001; KAHN1997; LIN1997) met the eligibility criteria, providing data on 198 participants. Two RCTs (GHODSE1994; SAN1994) compared clonidine or guanfacine versus placebo as an adjunct to tapered methadone detoxification, providing data on 230 participants. All were published in peer-reviewed journals (see Table 11 and Table 12 for further details on study information, critical outcomes and overall quality of evidence). The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 11: Study information and summary evidence table for trials of alpha$_2$ adrenergic agonists in opioid detoxification

	Lofexidine versus clonidine	**Methadone with alpha$_2$ adrenergic agonists versus methadone alone**
Total no. of trials (total no. of participants)	4 RCTs (N = 198)	2 RCTs (N = 230)
Study ID	CARNWATH1998 GERRA2001 KAHN1997 LIN1997	Clonidine: GHODSE1994 Guanfacine: SAN1994
Diagnosis	Opioid dependence: all Heroin: 100% (LIN1997) MMT: 64.8% (CARNWATH1998) Injection drug use: 56.4% (CARNWATH1998), 88% (LIN1997) Polydrug use: 35.7% (KAHN1997), 17.5% (methamphetamine; LIN1997)	Opioid dependence: all Heroin: 100% (SAN1994) MMT: 100% (GHODSE1994) HIV positive: 52% (SAN1994)
Mean years of opioid use	6.9 (CARNWATH1998), 3–6 (GERRA2001)	Not reported
Mean daily opioid use	Heroin: 1.5–2.0 g (GERRA2001), 1.05 g (LIN1997)	Heroin: 0.66 g (SAN1994) Methadone dose at entry: 35.1 mg (GHODSE1994)
Treatment length	3 days: GERRA2001 6 days: LIN1997 12 days: CARNWATH1998 18 days: KAHN1997	14 days: GHODSE1994 18 days: SAN1994

Continued

Table 11: (*Continued*)

	Lofexidine versus clonidine	**Methadone with alpha$_2$ adrenergic agonists versus methadone alone**
Length of follow-up	Up to 3 months	None
Age	20–32 years	25–27 years
Evidence profile table number (Appendix 17)	Table A17-8	Table A17-9
Overall quality of evidence	Moderate	Moderate
Benefits		
Abstinence	*1-month follow-up*: 65% versus 50%, RR 1.31 (0.80 to 2.13) K = 1, N = 50	—
Completion of treatment	76% versus 66%, RR 1.16 (0.90 to 1.50) K = 2, N = 90	52% versus 53%, RR 0.98 (0.77 to 1.25) K = 2, N = 230
Started naltrexone maintenance	RR 1.08 (0.70 to 1.66) K = 1, N = 40	—
Harms		
Adverse events	*Hypotension*: RR 0.72 (0.48 to 1.08) K = 2, N = 108 *Serious adverse events*: RR 0.11 (0.01 to 1.89) K = 1, N = 28	*Left study early due to hypotension*: RR 9.43 (1.25–71.24) K = 1, N = 86

For benefits, RR $>$ 1 favours lofexidine, or methadone with alpha$_2$ adrenergic agonists. For adverse events, RR $<$ 1 favours lofexidine, or methadone with alpha$_2$ adrenergic agonists.

Table 12: Adjunct medications, symptoms and adverse events for alpha$_2$ adrenergic agonists in opioid detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Lofexidine versus clonidine (RCTs)			
CARNWATH1998	**Lofexidine** versus **clonidine** for patients previously undergoing MMT (<40 mg) or using heroin – stopped abruptly at start of detoxification 0.2 mg versus 0.1 mg – up to 8 capsules	Clonazepam (0.5 mg four times daily), nitrazepam (10 mg), hyoscine (20 mg four times daily). If participants had been taking benzodiazepines, they were given equivalents in clonazepam. No further description.	Hypotension was greater with clonidine. No difference on the Short Opiate Withdrawal Scale between lofexidine and clonidine. No further description. Comment: Patients were asked if symptoms were side effects of the drug or due to withdrawal. Some went back onto MMT at end – there is some ambiguity concerning whether the aim of the detoxification was abstinence or just stabilisation.
GERRA2001	**Lofexidine** (1.2–1.6 mg) versus **clonidine**	Oral oxazepam (60 mg twice daily), oral baclofen (10 mg three times daily, for muscle relaxation), ketoprofene IV (400 mg, non-steroidal analgesic). All participants received naloxone IV (0.04 mg) and naltrexone (5 mg) on 2nd day.	Measured blood pressure: systolic blood pressure significantly lower in clonidine group than lofexidine group throughout 3 days of detoxification. 'Clonidine patients showed some withdrawal symptoms of moderate intensity (tremor, anxiety, tachycardia, insomnia) that disappeared after a few hours of clonidine oral administration.'

Continued

Table 12: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
KAHN1997	**Lofexidine** (0.4 mg) versus **clonidine** (0.2–1.8 mg) for patients previously undergoing MMT (stopped on day 3)	Clonidine group: eight patients received regular psychoactive medication: three nitrazepam, four temazepam, one temazepam + thioridazine (against protocol). Lofexidine group – five patients: one nitrazepam, four temazepam. No doses or frequency mentioned. For acute anxiety or agitation, additional medication (lorazepam) was available. Used by ten patients in each group: on 71 occasions in lofexidine group (126 mg total), 72 in clonidine group (148.5 mg total).	Mentions side effects – no difference between groups; most problematic were pain and insomnia. Total number of AEs: clonidine = 226, lofexidine = 114. Hypotension was less frequent for lofexidine (93% versus 53%, not significant). More reports of depression with clonidine and sedation. Clinicians recorded AEs that impacted on patient functioning: four patients, all clonidine; no further description. Comment: there was some ambiguity in distinguishing whether the reported symptoms were due to withdrawal from opioids or adverse effects of the medication used for detoxification.

LIN1997	**Lofexidine** (0.2 mg) versus **clonidine** (0.075 mg, four to eight times daily) for dependent heroin users	Lorazepam (1–2 mg four times daily). Flunitrazepam (4–8 mg nocte).	Hypotension: no differences between groups, and equals numbers of times medication withheld. However, if numbers of patients taken into account, then greater with clonidine. Withdrawal symptoms: no differences between lofexidine and clonidine. Comment: there was some ambiguity concerning whether medication was withheld due to hypotension or withdrawal symptoms.
Methadone with alpha$_2$ adrenergic agonists verus methadone alone (RCTs)			
GHODSE1994	**Clonidine** (0.2–1.2 mg) versus **methadone** (~60 mg)	Not mentioned.	Ten participants left the study early due to hypotension. Of these, nine were in the clonidine group (out of a total of 42 participants). Comment: No difference in side-effect profile.
SAN1994	**Methadone** versus **methadone + guanfacine (GFN) –** GFN-1 group: 3 mg; GFN-2 group: 4 mg. Methadone dosages were individually titrated at start to body weight and amount of heroin used, but by day 8 methadone group tapered to 10% of starting dose, and GFN-1 and GFN-2 to 50%.	59% given benzodiazepines for anxiety, and 32% as hypnotics. Mean dose of diazepam was 19.0 mg for methadone group; 20.3 mg for GFN-1, 16.3 mg for GFN-2. No frequency or duration of administration reported.	Similar decreases in blood pressure in methadone and GFN-1 groups. Greater reduction in GFN-2 groups (day 13 when 4 mg reduced to 2 mg). No pre-post difference in heart rate in methadone or GFN-1, but bradycardia in GFN-2. Comment: Asthenia – either side effect of guanfacine or withdrawal symptom. 'Low' doses of methadone: 38 mg.

No difference in efficacy was found between clonidine and lofexidine. Although the meta-analysis also found no significant difference in adverse event profiles (possibly due to a lack of statistical power), there was a strong trend associated with increased hypotension for participants receiving clonidine. It was also apparent that a wide range of adjunct medications were being used with alpha$_2$ adrenergic agonists in a majority of studies to ameliorate remaining withdrawal symptoms. However, generally there was not a full description of which medication was used, and therefore it was not possible to take this fully into account in the comparison.

Adding clonidine or guanfacine to a methadone taper did not improve efficacy of detoxification, but in one study clonidine significantly increased the occurrence of hypotension.

6.2.8 Adjunctive and other medications

The term 'adjunctive medication' covers a wide range of medications used to ameliorate symptoms of opioid withdrawal when used in addition to or instead of an opioid agonist (see 6.2.1). Adjunctive medication can target specific symptoms (such as diarrhoea), a collection of symptoms (such as insomnia and agitation), or, as with clonidine and lofexidine, hyperactivity in the noradrenaline system, which mediates a cluster of symptoms.

Alpha$_2$ adrenergic agonists
The evidence for alpha$_2$ adrenergic agonists is described in 6.2.7.

Benzodiazepines
Although benzodiazepines are often prescribed as an adjunct during detoxification to treat a range of symptoms such as insomnia, anxiety or agitation, the efficacy of two benzodiazepines compared with an opioid agonist for opioid detoxification has been studied. One study (DRUMMOND1989) compared chlordiazepoxide with methadone and another oxazepam with buprenorphine (SCHNEIDER2000). In the latter study, both groups also received carbamazepine. Both studies had small sample sizes providing data on 51 participants in total.

Evidence from critical outcomes and overall quality of evidence are presented in Table 13. The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively. The meta-analysis failed to find a difference between the use of benzodiazepines and opioid agonists for completion of detoxification treatment (see Table 13).

Alternatively, two studies have investigated the use of a benzodiazepine as an adjunct to a reducing methadone regimen. One placebo-controlled crossover study compared diazepam with doxepin, a tricyclic antidepressant, as an adjunct in outpatient methadone detoxification (McCaul *et al.*, 1984). Participants were randomised to receive diazepam (n = 10) or doxepin (n = 13) over the 10-week methadone taper period, and initially received their assigned medication in a range of doses, in a random order. In the final 4 weeks of detoxification, participants could self-administer the assigned medication in an intermediate dose, which could then be titrated. A greater

Table 13: Study information and summary evidence table for trials of benzodiazepines for opioid detoxification

	Opioid agonists versus benzodiazepines
Total no. of trials (total no. of participants)	2 RCTs (N = 51)
Study ID	Chlordiazepoxide versus methadone: DRUMMOND1989 Oxazepam versus buprenorphine: SCHNEIDER2000
Diagnosis	Opioid dependence
Mean years of opioid use	4.7 (DRUMMOND1989), 10.1 (SCHNEIDER2000)
Mean daily opioid use	Heroin: 0.8 g (DRUMMOND1989)
Treatment length	13 days: DRUMMOND1989 21 days: SCHNEIDER2000
Length of follow-up	None
Age	24–31 years
Evidence profile table number (Appendix 17)	Table A17-10
Overall quality of evidence	Low
Benefits	
Completion of treatment	57% versus 48%, RR 1.19 (0.71 to 1.98) K = 2, N = 50

RR > 1 favours opioid agonists.

proportion (RR = 6.50; 95% CI 0.90 to 47.19) of the diazepam group (five of ten) completed detoxification in comparison with the doxepin group (1 of 13), who also presented a greater proportion of opioid-positive urines throughout detoxification. However, given the wide scope for within-group variability in dosing schedules, it is not possible to draw any firm conclusions from the above findings.

Preston and colleagues (1984) also conducted a placebo-controlled crossover study, comparing oxazepam and clonidine as adjuncts to methadone detoxification. Six participants were assigned to each group on the basis of baseline characteristics. During each 5-day period for 30 days, participants received their assigned medication (oxazepam 20 mg/day, or clonidine 0.2 mg/day) and placebo capsules, in a random order. Participants then received either capsule of their choice. All participants were tapered from 50 mg methadone to zero over the first 15 days of the study. The authors

found that neither clonidine nor oxazepam significantly reduced withdrawal severity relative to their respective placebo control conditions, and likewise self-administration of the active medications had no effect on withdrawal severity.

Carbamazepine
Carbamazepine, an anticonvulsant, can be used to treat alcohol or benzodiazepine withdrawal (Schweizer *et al.*, 1991) and has been studied in cocaine dependence (though not found to be effective; Lima Reisser *et al.*, 2002) as well as being used for a variety of neuropsychiatric conditions. Therefore, the rationale of using it as an adjunct in opioid detoxification is to ascertain whether carbamazepine improved outcome in polydrug users. Two studies have given carbamazepine to all patients when comparing methadone and buprenorphine detoxification (SEIFERT2002) and when comparing oxazepam and clonidine as adjuncts in methadone detoxification (SCHNEIDER2000). However, in neither study was there a group not given carbamazepine, thus it is not possible to deduce if it does improve outcome in polydrug users.

6.2.9 Dosages and durations of detoxification

Information about databases searched and the inclusion/exclusion criteria used for this guideline can be found in Table 14. The efficacy of substitute (for example, methadone or buprenorphine) and adjunctive (for example, alpha$_2$ adrenergic agonists) medications

Table 14: Databases searched and inclusion/exclusion criteria for clinical effectiveness of dosage, duration and regulation of detoxification

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005 to January 2007
Study design	RCT
Patient population	Opioid dependent
Interventions	Pharmacological medication: methadone, buprenorphine, other opioid agonists, alpha$_2$ adrenergic agonists, opioid antagonists, sedatives (including benzodiazepines and Z-drugs) Dosage of medication: low, moderate, high starting dose Duration of detoxification: short, moderate, long Regulation of dosage schedule: linear schedule, exponential schedule; service user preference, provision of information to service user about schedule
Outcomes	Abstinence, treatment completion, safety/adverse events, severity of withdrawal

has been assessed above. This section examines whether the duration or rate of reduction of substitute or dose of adjunctive medication contributes to the outcome of detoxification (that is, abstinence/ completion of detoxification as assessed above).

Dosage of methadone

Table 15 summarises study information and evidence from studies comparing high and moderate starting doses. The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 15: Study information and summary evidence table for trials of methadone dosages in detoxification

	Methadone: high dose (80–100 mg) versus moderate dose (40–50 mg)
Total no. of trials (total no. of participants)	2 RCTs (N = 135)
Study ID	BANYS1994 STRAIN1999
Diagnosis	Opioid dependence
Mean opioid use	No data (BANYS1994) 25.3 times in last 30 days (STRAIN1999)
Treatment length	70 days: STRAIN1999 78 days: BANYS1994
Length of follow-up	None
Age	18–65
Evidence profile table number (Appendix 17)	Table A17-11
Overall quality of evidence	Moderate
Benefits	
Abstinence	*Proportion opioid-positive urines during treatment*: SMD −0.59 (−0.97 to −0.21) K = 1, N = 111
Completion of treatment	32% versus 22%, RR 1.45 (0.83 to 2.54) K = 2, N = 142

RR > 1 and negative SMD favours high dose.

In both studies participants were on methadone and on what may be considered as slow taper regimens, consisting of a 6-month stabilisation phase followed by a detoxification phase of 70 days (STRAIN1999) or 78 days (BANYS1994). It appears that for this type of detoxification regimen, beginning with a high dose of methadone at the stabilisation phase is more effective than a moderate dose and that this continues to affect abstinence during treatment and completion of detoxification.

Duration of methadone taper

Three double-blind RCTs compared different durations of methadone detoxification.

Senay and colleagues (1981) randomised participants to an 84-day methadone taper (n = 37), or a 21-day taper followed by placebo for the remainder of the study period (n = 35). The two groups did not differ in completion rate or abstinence at the end of the active medication period, or abstinence at 1-year follow-up. Sorensen and colleagues (1982) similarly found no significant difference in completion rate for a 21-day methadone taper (n = 15) versus a 42-day methadone taper (n = 18).

Stitzer and colleagues (1984) randomised participants undergoing a 90-day detoxification programme to taper from 60 mg methadone over 70 days (n = 13), or from 30 mg over 28 days (n = 13). There was no significant difference between groups in treatment retention.

In addition, one quasi-experimental study conducted by Gossop and colleagues (1989) in two inpatient detoxification facilities in London compared a 10-day methadone taper (n = 50) against a 21-day methadone taper (n = 82). The 10-day group reported a significantly higher peak withdrawal score on the OWS than the 21-day group ($t = 1.79$, $p < 0.05$), although there was no significant difference in the total duration of withdrawal symptoms. The two groups also did not differ in completion rate for detoxification (70.5% for the 10-day group, and 78.8% for the 21-day group; RR = 0.88, 95% CI = 0.71 to 1.09).

Regulation of methadone dosage schedules

There are a variety of ways to manage dosage schedules during methadone detoxification. The effects of providing information to the service user about the dosage schedule, the service user regulating the schedule, and schedules fixed by the clinician (for example, linear and exponential reduction) will be assessed. Three RCTs were identified that compared different ways of managing dosage schedules for methadone detoxification.

In a study lasting 42 days, Dawe and colleagues (1991) randomised participants to a fixed schedule methadone taper (n = 15), or were allowed to regulate their own dosage schedule with the aim of completing detoxification (that is, reaching zero dose) within the study period (n = 24). The fixed group were significantly more likely to complete detoxification (53% versus 17%, $\chi^2 = 4.49$, $p < 0.05$), and in a significantly shorter time frame (35 days versus 47 days, $t = 1.97$, $p < 0.05$). However, urinalysis suggested no significant difference between groups in illicit opioid use at 6-week follow-up.

Green and Gossop (1988) randomised participants undergoing a 21-day methadone taper to the 'informed group' (n = 15), who received detailed information about aspects of the detoxification programme such as dosages and expected symptomatology, and the 'uninformed group' (n = 15), who received a routine clinical

interview. The informed group were more likely to complete detoxification (46.7% versus 80.0%, $\chi^2 = 32.12$, $p < 0.01$), and reported significantly lower withdrawal scores on the final day of detoxification ($t = 2.48$, $p < 0.05$) as well as over the 25-day post-detoxification period ($F = 3.93$, $p < 0.05$).

Strang and Gossop (1990) randomised participants undergoing a 10-day methadone detoxification programme to a linear ($n = 43$) or exponential ($n = 44$) taper schedule. Both groups were equally likely (84%) to complete detoxification but the exponential group reported significantly higher withdrawal severity on the OWS during the acute phase of withdrawal ($F = 4.34$, $p < 0.05$).

Dosage and duration of buprenorphine detoxification

The typical duration of detoxification using buprenorphine is between 4 and 8 days. There is one RCT (Assadi *et al.*, 2004) that compared regimens using a high dose of buprenorphine in the first 24 hours only, with a more typical regimen reducing buprenorphine over 5 days. At high doses, buprenorphine may effectively act as an antagonist and hence precipitate withdrawal. Buprenorphine was given intramuscularly; the high dose (12 mg; 6×1.5 mg doses) was equivalent to 21.3 mg sublingual and the reducing regimen started at 1.5 mg of intramuscular buprenorphine twice a day. No significant differences in treatment retention, successful detoxification (negative naloxone challenge test) or severity of withdrawal were reported. Adjunctive medications (trazodone and indomethacin) were used more by the high-dose group than when buprenorphine was reduced with equal amounts of the others (diazepam, chlorpromazine and hyoscine).

Dosage schedules for alpha$_2$ adrenergic agonists

No studies were found comparing different dosage schedules of clonidine or lofexidine, however a variety of regimens were reported in the included studies (see Table 12), with some continuing substitute prescribing for a few days when starting the alpha$_2$ adrenergic agonist, and in other studies it was stopped at that time. Doses of alpha$_2$ adrenergic agonists were generally increased over 3 days depending on acceptability and control of withdrawal symptoms, maintained for a period then tapered over approximately 3 days at the end.

Clinical summary

For methadone, a high starting dose (80–100 mg/day) appeared to be superior to a standard starting dose (40–50 mg/day) in abstinence (opioid-negative urinalyses during treatment) and completion outcomes, although it may be argued whether abstinence during treatment is a meaningful outcome in this context, given that a higher methadone dose would be expected to reduce the desire to use additional illicit opioids. Improved completion rates could be the result of participants being better stabilised at the outset on a higher dose.

Regarding the duration of detoxification, neither a long methadone taper (up to 70 days) nor a fairly short programme (14 days) was any better than a standard 21-day taper. Also, keeping service users fully informed about different aspects of detoxification appears to have some effect in improving completion rates and minimising reported withdrawal severity.

There is a lack of data assessing dosage and duration for detoxification using buprenorphine or alpha$_2$ adrenergic agonists. Therefore it is not yet possible to draw conclusions on these issues at present.

6.3 OVERALL CLINICAL SUMMARY OF PHARMACOLOGICAL INTERVENTIONS IN DETOXIFICATION

For all sub-sections there were too few studies in each meta-analysis to check for publication bias using funnel plots. However, publication bias is possible as the GDG and review team had access to only very limited unpublished data.

Opioid agonists
Methadone and buprenorphine both appeared to be effective in comparison with other detoxification treatments such as alpha$_2$ adrenergic agonists and other opioid agonists. Dihydrocodeine did not appear to be effective in comparison with buprenorphine. However, it is not clear if there is any difference in efficacy between methadone and buprenorphine for detoxification.

Alpha$_2$ adrenergic agonists
There were no differences found in completion of detoxification between clonidine and lofexidine. However, clonidine was associated with higher levels of hypotension. It was also apparent that a wide range of adjunct medications was being used with alpha$_2$ adrenergic agonists in a majority of studies to ameliorate remaining withdrawal symptoms, although this was not well reported.

Side effects and adverse events
Among the reviewed studies there was heterogeneity in how withdrawal symptoms, side effects or adverse events were described and attributed. In addition, without a full description of adjunctive medication taken, it was often not possible to delineate further how to attribute a sign or symptom. Aside from hypotension, which was recognised as a side effect or adverse event associated with clonidine (see above), the majority of other signs or symptoms were consistent with those expected from opioid withdrawal and often were non-specific.

6.4 CLINICAL PRACTICE RECOMMENDATIONS

6.4.1 The use of opioid agonists

6.4.1.1 Methadone or buprenorphine should be offered as the first-line treatment in opioid detoxification. When deciding between these medications, healthcare professionals should take into account:

- whether the service user is receiving maintenance treatment with methadone or buprenorphine; if so, opioid detoxification should normally be started with the same medication
- the preference of the service user.

6.4.1.2 Dihydrocodeine should not be used routinely in opioid detoxification.

6.4.2 Use of adjunctive medications in opioid detoxification

6.4.2.1 Lofexidine may be considered for people:

- who have made an informed and clinically appropriate decision not to use methadone or buprenorphine for detoxification
- who have made an informed and clinically appropriate decision to detoxify within a short time period
- with mild or uncertain dependence (including young people).

6.4.2.2 Clonidine should not be used routinely in opioid detoxification.

6.4.2.3 When prescribing adjunctive medications during opioid detoxification, healthcare professionals should:

- only use them when clinically indicated, such as when agitation, nausea, insomnia, pain and/or diarrhoea are present
- use the minimum effective dosage and number of drugs needed to manage symptoms
- be alert to the risks of adjunctive medications, as well as interactions between them and with the opioid agonist.

6.4.3 Dosage and duration of detoxification

6.4.3.1 When determining the starting dose, duration and regimen (for example, linear or stepped) of opioid detoxification, healthcare professionals, in discussion with the service user, should take into account the:

- severity of dependence (particular caution should be exercised where there is uncertainty about dependence)
- stability of the service user (including polydrug and alcohol use, and comorbid mental health problems)
- pharmacology of the chosen detoxification medication and any adjunctive medication
- setting in which detoxification is conducted.

6.4.3.2 The duration of opioid detoxification should normally be up to 4 weeks in an inpatient/residential setting and up to 12 weeks in a community setting.

6.4.4 Research recommendation – adjunctive medication during detoxification

6.4.4.1 If a person needs adjunctive medication during detoxification, in addition to their opioid agonist reducing regimen or in addition to an adjunctive alpha-2 adrenergic agonist (for example, lofexidine), what medications are associated with greater safety and fewer withdrawal symptoms?

Why this is important
A large variety of adjunctive medications are used for the management of withdrawal symptoms during detoxification, particularly when alpha-2 adrenergic agonists are used. Research is needed to guide decisions on how best to manage withdrawal symptoms with minimal risk of harm to the service user.

6.5 ULTRA-RAPID, RAPID AND ACCELERATED DETOXIFICATION USING OPIOID ANTAGONISTS

6.5.1 Introduction

Ultra-rapid and rapid detoxification are approaches for detoxifying opioid-dependent patients using opioid antagonists, such as naloxone, naltrexone or nalmefene, typically under general anaesthesia or heavy sedation. The aim is to flood the brain with an opioid antagonist to remove all agonists very rapidly while the anaesthesia or sedation minimises discomfort. The patient is then maintained on naltrexone, which has led some to refer to this as 'rapid antagonist induction'.

A variety of protocols have been used, with the essential distinctions between ultra-rapid and rapid detoxification being the duration of detoxification and the level of sedation. In ultra-rapid detoxification, patients are admitted to intensive care units or high dependency units for 24 hours (therefore, not routine inpatient addiction facilities) and receive naltrexone or naloxone to precipitate withdrawal; anaesthesia is initiated as withdrawal symptoms emerge, and is maintained for 5–6 hours using various medications in addition to those for controlling opioid withdrawal. In rapid detoxification, instead of anaesthesia, sedation with a benzodiazepine (most commonly midazolam) is used, but otherwise the medications used are broadly similar. The typical duration is 1–5 days.

Others, however, have also referred to ultra-rapid detoxification more widely as including the use of heavy sedation, and rapid detoxification when an opioid antagonist is used to precipitate withdrawal in awake patients (O'Connor & Kosten, 1998).

The reported advantage of using ultra-rapid or rapid detoxification with anaesthesia or sedation is that the duration of withdrawal symptoms is shortened and discomfort is minimised through the anaesthesia or sedation. Since it was reported in the late 1980s (Loimer *et al.*, 1989), the technique and medications used have evolved. It has also courted controversy; the main issues with such an approach involve the high degree of risk, including fatalities. This is particularly striking given that opioid withdrawal alone rarely results in death. Furthermore, the associated costs required to give the appropriate medical support are much greater than for other methods of detoxification. There has been much debate over its effectiveness, with limited long-term outcome data available.

Alternatively, naltrexone and naloxone have been used in addition to clonidine, lofexidine or buprenorphine to speed up or shorten detoxification without precipitating full withdrawal; this is referred to here as accelerated detoxification. Note that such use of naltrexone and naloxone has been considered distinct from the use of adjunctive medications as defined here, since opioid antagonists do not actually ameliorate

withdrawal symptoms. The service user is not sedated, or only minimally. This approach may also help establish service users on naltrexone for preventing relapse.

Current practice
In the UK, ultra-rapid and rapid detoxification with anaesthesia or sedation are not offered within the NHS but appear to occur in the private sector. They are also available in some parts of Europe (such as Spain, Switzerland and the Netherlands) and Australia (Mattick *et al.*, 2001).

The uses of naltrexone or naloxone to accelerate detoxification appear to be uncommon in specialist drug services in the UK (Day *et al.*, 2005).

6.5.2 Definitions of levels of sedation

Minimal or light sedation
Minimal or light sedation involves the administration of medication in order to deal with anxiety, insomnia or agitation. The defining characteristic of this type of sedation is that the person still appears relatively awake and is able to communicate clearly at all times. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. This type of sedation is usually not sufficient for a significant procedure or painful intervention to occur. Most studies of 'conventional' detoxification in which adjunct sedative medications are prescribed fall under this classification (see Section 6.2).

Moderate sedation
During moderate sedation, a higher level of sedation than minimal or light sedation, the person appears obviously sedated, but importantly can maintain an open airway independently and respond purposefully to stimuli (such as verbal questioning).

Deep sedation (or heavy sedation)
During deep sedation (or heavy sedation), an even higher level of sedation, the person is clearly sedated, may not be easily aroused or respond purposefully to verbal commands, and may only respond minimally to very significant stimuli (such as high levels of pain). A person may experience partial or complete loss of protective reflexes, including the ability to maintain an open airway independently and continuously. He or she may therefore require assistance in maintaining an open airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

While deep sedation may not equate to general anaesthesia, there is a consensus that its supervision requires the same level of training and skill (The Royal College of Anaesthetists, 2001). If verbal responsiveness is lost, the person requires a level of care identical to that needed for general anaesthesia.

General anaesthesia
Under general anaesthesia a person is unconscious and unresponsive, even in the face of significant stimuli. The ability to maintain ventilatory function independently is

often impaired. The person often requires assistance in maintaining an open airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

6.5.3 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/ exclusion criteria used for this section of the guideline can be found in Table 16.

Table 16: Databases searched and inclusion/exclusion criteria for clinical effectiveness of rapid and ultra-rapid detoxification under sedation and/or general anaesthesia

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005–January 2007
Study design	RCT
Patient population	Adults and young people who are opioid dependent
Interventions	Opioid antagonist-accelerated detoxification under minimal or light sedation, rapid detoxification under moderate sedation, ultra-rapid detoxification under general anaesthesia or deep sedation
Outcomes	Abstinence, treatment completion, safety/adverse events, severity of withdrawal

6.5.4 Studies considered[6]

The review team conducted a new systematic search for RCTs that assessed the efficacy and safety of ultra-rapid and rapid detoxification under sedation and/or general anaesthesia. In addition, a further search for observational studies was undertaken to assess the safety of ultra-rapid and rapid detoxification under sedation and/or general anaesthesia.

[6]Here, and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

6.5.5 Opioid antagonist-accelerated detoxification under minimal or light sedation

For comparisons of naltrexone/naloxone versus placebo as an adjunct to buprenorphine, clonidine or lofexidine detoxification, five RCTs (GERRA1995; GERRA2000; O'CONNOR1997; BESWICK2003A; UMBRICHT1999) met the eligibility criteria, providing data on 399 participants (for further details on study information, evidence from critical outcomes and overall quality of evidence see Table 17 and Table 18). The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 17: Study information and summary evidence table for trials of opioid antagonist-accelerated detoxification under minimal or light sedation

	Opioid antagonist-accelerated detoxification versus detoxification without opioid agonists
Total no. of trials (total no. of participants)	5 RCTs (N = 399)
Study ID	Naloxone with lofexidine: BESWICK2003A Naltrexone with clonidine: GERRA1995 GERRA2000 O'CONNOR1997 Naltrexone with buprenorphine: UMBRICHT1999
Diagnosis	Opioid dependence: all Heroin: 100% (GERRA1995) Injection drug use: 30% (UMBRICHT1999)
Mean years of opioid use	Heroin: 2–4 (GERRA1995), 2– 6 (GERRA2000), 6.5–8.3 (UMBRICHT1999), 7.7–8.9 (O'CONNOR1997)
Mean daily opioid use	Heroin: 0.5 g (GERRA1995), 0.55 g (BESWICK2003), 1.5–2.0 g (street heroin; GERRA2000) Bags of heroin in past 30 days: 3.8–4.0 (O'CONNOR1997) Days of heroin use in past 30 days: 29 (UMBRICHT1999) Methadone dose at entry (mg/day): 41.9 (BESWICK2003A)

Continued

Table 17: (*Continued*)

	Opioid antagonist-accelerated detoxification versus detoxification without opioid agonists
Treatment length	4 days: GERRA1995 6 days: BESWICK2003A 8 days: O'CONNOR1997, UMBRICHT1999
Length of follow-up	Up to 6 months
Age	18–56 years
Evidence profile table number (Appendix 17)	Table A17–12
Overall quality of evidence	Moderate
Benefits	
Abstinence	*Abstinent at 6-month follow-up:* 44% versus 53%, RR 0.82 (0.49 to 1.37) K = 1, N = 64 *Maintained abstinence throughout at 9-month follow-up*: 20% versus 9%, RR 2.30 (0.76 to 6.94) K = 1, N = 91 *Abstinent in past month at 9-month follow-up:* 36% versus 26%, RR 1.36 (0.73 to 2.55) K = 1, N = 91
Completion of treatment	78% versus 77%, RR 1.01 (0.86 to 1.17) K = 4, N = 335
Concordance with naltrexone maintenance at 3-month follow-up	75% versus 53%, RR 1.41 (0.96 to 2.07) K = 1, N = 64
Self-rated withdrawal severity	*Peak*: SMD 0.95 (−1.20 to 3.10) K = 2, N = 184 *Overall*: SMD 0.51 (−0.58 to 1.60) K = 2, N = 162 *Left study early due to withdrawal:* RR 1.75 (0.35 to 8.84) K = 1, N = 60

For abstinence, completion and starting naltrexone maintenance, RR > 1 favours naltrexone/naloxone. For drug use and leaving study early, RR < 1 favours naltrexone/naloxone. For withdrawal severity, negative SMD favours naltrexone/naloxone.

Table 18: Adjunct medications, symptoms and adverse events for opioid antagonists in opioid detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
Opioid antagonist-accelerated detoxification under minimal/light sedation versus detoxification without opioid antagonists (RCTs)			
BESWICK2003A	**Lofexidine** (1.8 mg) **with naloxone** (0.8 mg) versus **lofexidine with placebo**	Prochlorperazine (5 mg) given at start to alleviate nausea. Diazepam available as required evening before first dose of study medication (5 mg) and daily (max 15–20 mg) thereafter to reduce anxiety and restlessness. Additional lofexidine (up to 0.4 mg/day) available during any 24 hours upon request.	Measured withdrawal using Short Opiate Withdrawal Scale – scores were higher in the naloxone group after receiving naloxone but only significantly on the 3rd day 1 hour after the injection, and then at times on days 5, 6, 7 and 8. More diazepam was used in the naloxone group on the 3rd and 4th days but not on other days.
GERRA1995	**Clonidine with naltrexone** versus **clonidine with placebo**	Not mentioned.	List of nine observer-rated signs of withdrawal: pulse rate, tremors, rhinorrhoea, mydriasis, aching muscles, shiver, vomiting, anxiety, insomnia.
GERRA2000	See Table 5 [methadone]		
O'CONNOR1997	See Table 8 [buprenorphine]		

Continued

Table 18: (*Continued*)

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
UMBRICHT1999	**Buprenorphine with naltrexone** versus **buprenorphine with placebo**	A range of medications according to 'standard indications' for withdrawal symptoms, initiated when Objective Opiate Withdrawal Scale is 5 or greater. Included: clonidine (83% of participants), hydroxyzine (77%), diazepam (25%), ibuprofen (50%), acetaminophen (78%), dicyclomine (43%), diphenoxylate (35%). 16% in each group required no adjuncts. Mean and dose ranges given; significantly more participants in naltrexone group received hydroxyzine, and significantly higher doses of ibuprofen also used in this group.	Measured withdrawal using Objective Opiate Withdrawal Scale. Among drop-outs, four participants in naltrexone group gave withdrawal as reason (including one abdominal pain), one from placebo group experienced severe buprenorphine-induced withdrawal, and acknowledged having used methadone just before admission. Regarding physiological measures including pupil size, heart rate and blood pressure: 'It cannot be excluded that adjunct medication used for withdrawal management on day 2 and day 8 may have blunted differences between groups'.

In this approach, unlike ultra-rapid and rapid detoxification regimens using opioid antagonists to precipitate full withdrawal (see Sections 6.5.6 and 6.5.7), detoxification had already commenced (BESWICK2003A; GERRA1995) and/or a low dose of the opioid antagonist was given (O'CONNOR1997; UMBRICHT1999). In addition, in these protocols, other adjunct medication was used or available, such as clonidine and benzodiazepines. Using a low dose of naltrexone (12.5 mg) is different from the so-called 'Asturian method', where 50 mg of naltrexone is given at the start with a greater range and higher doses of medication to treat opioid withdrawal symptoms (Carreno *et al.*, 2002; see Section 6.5.6).

6.5.6 Rapid detoxification under moderate sedation

One RCT (ARNOLD-REED2005) comparing rapid detoxification under moderate sedation against detoxification under minimal or light sedation met the eligibility criteria, providing data on 80 participants. It was published in a peer-reviewed journal (for further details on study information, evidence from critical outcomes and overall quality of evidence see Table 19).

The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Asturian method

One approach, the 'Asturian method', has been used at home without direct medical or nursing supervision (Carreno *et al.*, 2002). Service users were requested to take no opioids for 12 hours before the procedure in order to reduce the severity of precipitated withdrawal. They were then moderately sedated using the following medication: 0.45 mg clonidine, 40 mg famotidine, 4 mg loperamide, 22.5 mg midazolam, 12 mg ondansetron and 50 mg clorazepate. After 45 minutes, they were then woken to receive 10 mg metoclopramide and 50 mg naltrexone to precipitate withdrawal. After 1 hour 45 minutes, further symptomatic medication was provided (20 mg hyoscine butylbromide, 0.3 mg clonidine and 10 mg metocopramide). After 24 hours, service users were given a physical examination, medication to manage withdrawal symptoms was provided if needed, and individuals were inducted onto naltrexone maintenance treatment.

Carreno and colleagues (2002) reported a case series of 1,368 service users who had received the Asturian method. This report was primarily descriptive, with limited reporting of outcomes, and involved no comparison group; therefore conclusions drawn on the efficacy of this procedure are limited.

Table 19: Study information and summary evidence table for rapid detoxification under moderate sedation

	Rapid detoxification under moderate sedation versus detoxification under minimal/light sedation
Total no. of trials (total no. of participants)	1 RCT (N = 80)
Study ID	ARNOLD-REED2005
Diagnosis	Opioid dependence
Years of opioid use	Used heroin for more than 5 years: 66%
Daily opioid use	Daily heroin use: 95%
Treatment length	1 day (rapid detoxification under moderate sedation) versus 7–10 days (clonidine detoxification)
Length of follow-up	1 month
Mean age	30 years
Evidence profile table number (Appendix 17)	Table A17-14
Overall quality of evidence	Moderate
Benefits	
Abstinence	*1-month follow-up*: 39% versus 30%, RR 1.30 (0.59 to 2.84) K = 1, N = 80
Completion of treatment	88% versus 28%, RR = 3.11 (1.86 to 5.20) K = 1, N = 80
Concordance with naltrexone maintenance	Started 50 mg maintenance dose: 86% versus 50%, RR 1.72 (1.09 to 2.72) K = 1, N = 80 Achieved 100% concordance over 4-week follow-up: 56% versus 40%, RR 1.39 (0.75 to 2.56) K = 1, N = 80
Self-rated withdrawal severity	*Mean change from baseline (completers analysis)*: SMD −1.70 (−2.56 to −0.84) K = 1, N = 41

RR > 1 and negative SMD favour ultra-rapid detoxification.

6.5.7 Ultra-rapid detoxification under general anaesthesia or deep (or heavy) sedation

For comparisons of ultra-rapid detoxification under general anaesthesia or deep (or heavy) sedation against detoxification under minimal or no sedation, six RCTs (COLLINS2005; DE JONG2005; FAVRAT2006; KRABBE2003; MCGREGOR2002; SEOANE1997) met the eligibility criteria, providing data on 845 participants. In addition, one RCT (Hensel *et al*., 2000), one quasi-experimental study (Hoffman *et al.*, 1998), five case series (Armstrong *et al.*, 2003; Cucchia *et al.*, 1998; Elman *et al.*, 2001; Gold *et al.*, 1999; Hamilton *et al.*, 2002) and three case reports (Cook & Collins, 1998; Roozen *et al.*, 2002; Shreeram *et al.*, 2001) provided data on adverse events in ultra-rapid detoxification. All studies were published in peer-reviewed journals (for further details on study information, evidence from critical outcomes and overall quality of evidence see Table 20 and Table 21). The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 20: Study information and summary evidence table for trials of ultra-rapid opioid detoxification

	Ultra-rapid detoxification under general anaesthesia versus detoxification under light or minimal sedation
Total no. of trials (total no. of participants)	6 RCTs (N = 845)
Study ID	Propofol anaesthesia (versus clonidine without general anaesthesia): COLLINS2005 FAVRAT2006 MCGREGOR2002 Propofol anaesthesia (versus methadone without general anaesthesia): KRABBE2003 Propofol anaesthesia (versus naltrexone without general anaesthesia): DE JONG2005 Propofol with midazolam (versus light sedation with same agents): SEOANE1997
Diagnosis	Opioid dependence

Continued

Table 20: *(Continued)*

	Ultra-rapid detoxification under general anaesthesia versus detoxification under light or minimal sedation
Mean years of opioid use	Heroin: 6.3–11.1 (KRABBE2003), 9.9 (MCGREGOR2002), 12.0 (DEJONG2005) Lifetime heroin use disorder: 7.5 (COLLINS2005) Methadone: 3.5–9.4 (KRABBE2003)
Mean daily opioid use	Heroin (mg): 741.3 (SEOANE1997) Methadone (mg): 38.5–58.4 (KRABBE2003) Times heroin used in past 30 days: 87.1 (MCGREGOR2002) Days heroin used in past 30 days: 18.4 (DE JONG2005), 30 (COLLINS2005) Days methadone used in past 30 days: 22.8 (DE JONG2005)
Treatment length	1 day: SEOANE1997 1 day (ultra-rapid group) versus 7 days (control group): FAVRAT2006 3 days: COLLINS2005, MCGREGOR2002 7 days: DE JONG2005
Length of follow-up	Up to 12 months
Mean age	30–36 years
Evidence profile table number (Appendix 17)	Table A17-13
Overall quality of evidence	Moderate
Benefits	
Abstinence	*1-month follow-up*: 66% versus 58%, RR 1.54 (0.66 to 3.59) K = 2, N = 302 *3-month follow-up*: 30% versus 14%, RR 2.08 (1.18 to 3.68) K = 3, N = 169 *6-month follow-up:* 22% versus 8%, RR 2.70 (0.92 to 7.91) K = 1, N = 101 *12-month follow-up*: 20% versus 14%, RR 1.40 (0.58 to 3.39) K = 1, N = 101

Continued

Table 20: *(Continued)*

	Ultra-rapid detoxification under general anaesthesia versus detoxification under light or minimal sedation
Completion of treatment	84% versus 54%, RR = 1.67 (0.88 to 3.18) K = 4, N = 270
Concordance with naltrexone maintenance	Started 50 mg maintenance dose *Versus clonidine control group:* 61% versus 19%, RR 3.87 (1.03 to 14.54) K = 3, N = 240
	Versus naltrexone control group: 90% versus 99%, RR 0.91 (0.86 to 0.97) K = 1, N = 272
Harms	
Adverse events	*Serious adverse events:* RR 3.62 (1.36, 9.61) K = 3, N = 644

For benefits, RR $>$ 1 and negative SMD favour ultra-rapid detoxification. For adverse events, RR $<$ 1 favours ultra-rapid.

6.5.8 Clinical summary

There were too few studies in each meta-analysis to check for publication bias using funnel plots. However, publication bias is possible as the review team and the GDG did not have access to any unpublished data.

Accelerated detoxification under minimal or light sedation
Adding an opioid antagonist to clonidine, lofexidine or buprenorphine detoxification had no effect on completion rates, but showed a trend for increased withdrawal severity, as might be expected from a process that accelerates withdrawal. Data for abstinence at follow-up were inconsistent, with one study showing a trend favouring an opioid antagonist at 9-month follow-up while another study showed the opposite trend at 6-month follow-up.

Rapid detoxification under moderate sedation
No firm conclusions could be drawn from the limited evidence base concerning the safety and efficacy of this detoxification method. It was apparent however that precipitating withdrawal necessitated the polypharmacy of adjunct medications for managing symptoms; this is likely to carry inherent risks (for example, increased likelihood of medication interactions), particularly if detoxification occurs within a setting with minimal medical supervision (for example, at home).

Table 21: Adjunct medications, symptoms and adverse events for rapid and ultra-rapid detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Ultra-rapid detoxification under general anaesthesia or deep sedation (RCTs)			
COLLINS2005	**Anaesthesia-assisted** (propofol) versus **buprenorphine + clonidine** versus **clonidine with naltrexone induction**	Anaesthesia group – ranitidine, clonidine, midazolam, propofol, isoflurane, lidocaine, tubocurarine, succinylcholine, octreotide, naltrexone, ketorolac, ondansetron, neostigmine. 'Given as needed' in the buprenorphine and clonidine groups – ondansetron, ketorolac, octreotide, clonazepam, acetaminophen, magnesium hydroxide, aluminium hydroxide/magnesium hydroxide/simethicone.	Anaesthesia group: One case of aspiration pneumonia and upper airways oedema – 'had concealed' history of similar complications previously. One case of mixed bipolar state, was suicidal 5 days later – 'had concealed' history of bipolar disorder. One case of diabetic ketoacidosis 2 days after discharge – 'had concealed' previous such history. Comments: 'had concealed'– it is questionable whether participants concealing a history of psychiatric or physical health problems is an adequate explanation of the presence of adverse events.

DEJONG2005	**Rapid detoxification with general anaesthesia (RD-GA) versus without (RD) general anaesthesia:** naltrexone General anaesthesia: propofol, gallamine, octreotide	Clonidine (to reduce hypertension; 0.3 mg), diclofenac, ondansetron, diazepam (10 mg), nicotine patch, octreotide, butylscopolamine, haloperidol (1–3 mg prn), midazolam.	RD group – no AEs. RD-GA group – five cases, all of whom subsequently recovered: One treated for 'extreme drowsiness resulting from anaesthesia' (result of pre-existing liver metabolism problem due to hepatitis C?). One with previous psychiatric history, treated for agitation with propofol sedation (possible delirious psychotic episode due to detoxification and anaesthesia). One case of hypoxia – had a history of chronic obstructive pulmonary disease and pneumonia. One case of fever, cause unknown. One case of pneumonia – anaesthesia associated aspiration.
FAVRAT2006	**Ultra-rapid detoxification under anaesthesia** (propofol) – naltrexone, lidocaine (to deepen anaesthesia) Clonidine group – 0.6 mg in divided doses	Ultra-rapid group – clonidine (to control withdrawal), octreotide (for diarrhoea), ketorolac (analgesic/anti-inflammatory), droperidol (if delirious), neostigmine. Clonidine group – loperamide (4 mg for diarrhoea), tolperisone (150 mg for muscular aches), ondansetron (4 mg for nausea), zolpidem (10 mg for insomnia), olanzapine (5 mg for agitation), paracetamol (500 mg for headaches).	No description of AEs. 'No patients died or had severe complications'. One person in anaesthetic group died 3 months later 'probably of overdose but drug interactions or a somatic cause could not be excluded' – had relapsed and was taking methadone, benzodiazepine and an antidepressant; also had gastrointestinal bleeding.

Continued

Table 21: *(Continued)*

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
HENSEL2000	**Ultra-rapid detoxification under anaesthesia** – propofol (induction at 1.5–3 mg, maintained with 0.1–0.35 mg/kg), naltrexone Aim was to study using electroencephalogram (EEG) to measure withdrawal	Clonidine (2 mcg/kg/hour).	Stated that there were no anaesthetic complications, but then 'negligible side effects – depended on dose of propofol', which were significantly lower when EEG monitoring was used. Eight people had bradycardia and required treatment. One patient had a first degree heart arteriovenous AV block and required treatment. Six patients had mild but persistent hypotension (systolic blood pressure: 80–90 mmHg) and required treatment.
KRABBE2003	**Ultra-rapid detoxification under anaesthesia** (propofol) – oral naltrexone (100 mg) **Methadone** group – tapered to nil in 1 or 2 weeks	Ultra-rapid group only: premedication with diclofenac (50 mg), loperamide (8 mg), paracetamol (1000 mg), clonidine (0.3 mg), and tropisetron IV (5 mg). Withdrawal signs and symptoms treated parenterally with, for example. antiemetics, anti-diuretics and clonidine.	No mention of adverse events.

MCGREGOR; 2002	**Anaesthesia** (propofol) versus **inpatient ± naltrexone** Inpatient 'normal clinic practice'	Clonidine, octreotide. Inpatient – symptomatic medications: clonidine, diazepam, orphenadrine, paracetamol, temazepam, naproxen, metoclopramide, buscopan, vitamins.	In discussion – no serious AEs.
SEOANE1997	Ultra-rapid detoxification with **light** versus **deep sedation** Light – propofol, midazolam Deep – as above at higher doses	Clonidine, metoclopramide, naloxone/naltrexone.	97.3% discharged from hospital after 24 hrs; 2.3% (seven patients) delayed to 48 hours due to vomiting, diarrhoea and fever; one delayed to 5 days due to pneumonia. 'Overall complications rate was 4.3% (13 complications presented by 13 patients)', for example excessive sedation leading to respiratory depression (requiring intubation), bronchospasm and bradycardia.
Rapid and ultra-rapid detoxification (observational studies)			
Armstrong *et al.* (2003) *Retrospective case series*	Outpatient **naltrexone-accelerated detoxification**		Over a 6-month period, 42 patients presented to the emergency department following detoxification. Common symptoms were vomiting, diarrhoea, abdominal pain, agitation requiring sedation and excessive drowsiness. Most symptoms were managed with simple supportive care.

Continued

Table 21: ***(Continued)***

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
Cook & Collins (1998) *Case report*	**Ultra-rapid detoxification under general anaesthesia**		On reducing use, a 38 year old, an injecting heroin user for over 20 years, experienced shakiness, stomach cramps, cold sweats, visual hallucinations and formication (tactile hallucination). Detoxification resulted in mild hypertension, tachycardia and goosebumps. Also progressive fall in blood pressure, heart rate and temperature during procedure. Temperature was out of normal range, and was treated with a warming blanket. On waking, the service user was easily weaned off assisted ventilation and extubated, reported feeling 'fantastic' and remained opioid free for 11 months while receiving professional counselling.
Cucchia *et al.* (1998) *Case series*	**Oral naltrexone and midazolam with clonidine and ondansetron**, for heroin or methadone users	Dependent benzodiazepine users tended to need more benzodiazepines (diazepam equivalents = 255 ± 53 mg, versus 178 ± 89 mg), but difference not significant.	'No serious adverse event occurred during ultra-rapid opioid detoxification.' Mentions low blood pressure that needed no intervention; diarrhoea and vomiting in some participants. One patient with borderline personality disorder made a serious suicide attempt with antidepressants given by the clinician on the previous day.

Elman *et al.* (2001) *Case series*	**Ultra-rapid detoxification under general anaesthesia** Six participants had been maintained on methadone, one had been using transdermal fentanyl patches.		During anaesthesia phase, plasma adrenocorticotropic hormone and cortisol levels were markedly increased. During post-anaesthesia phase, marked withdrawal and rapid breathing occurred in all service users. Respiratory distress in one, but blood pressure and heart rate remained stable. During the post-detoxification phase (3 weeks) there were elevated withdrawal scores, minimal self-reported craving and gradual improvement in vegetative symptoms, anxiety and depression.
Gold *et al.* (1999) *Case series*	**Ultra-rapid detoxification under general anaesthesia** Premedication with glycopyrrolate and clonidine; anaesthesia with propofol and cisastracurium; detoxification with naloxone and nalmefene. Oral naltrexone induction at the end of procedure.	Clonidine and octreotide at start of protocol; ketorolac, midazolam and clonidine as needed, but anti-diarrhoeals were never actually prescribed.	'All 20 patients successfully completed detoxification without any adverse medical or anaesthetic events.' However, one patient (a 42-year-old man) was found dead approximately 41 hours after completion of the procedure. No information at bedside was apparent about the cause of death and no autopsy was performed at family's insistence; blood samples did not find evidence of inappropriate dosing or illicit drugs. Authors could not conclude whether this death was a result of the detoxification procedure.

Continued

Table 21: *(Continued)*

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
Hamilton *et al.* (2002) *Case series*	**Ultra-rapid detoxification under general anaesthesia**, with subcutaneous naltrexone pellets.		*Case 1:* Service user had acute dyspnoea, was agitated, yawning, had diarrhoea and diagnosed with acute pulmonary oedema. The pellet was removed and withdrawal symptoms resolved after 12 hours. *Case 2:* 27-year-old service user experienced 5 days of vomiting, diarrhoea, dry mouth, weakness, fatigue, poor urine output and hyperalgesia – all symptoms started immediately after detoxification. The pellet was removed on the service user's request. *Case 3:* During the entire post-detoxification period, the service user complained of intractable nausea and vomiting, which did not respond to antiemetics. Two weeks after detoxification, the service user presented at the emergency department still complaining of persistent nausea, vomiting, weakness, dry mouth, and poor urine output. The service user had weight loss of 15-20 pounds, chills, sneezing, coughing, anorexia and abdominal pain.

			The pellet was removed, after which the service user received treatment for dehydration and withdrawal symptoms. Within 24-hours the service user was tolerating an oral diet and discharged. *Case 4*: Six hours after detoxification, the service user was found unresponsive in bed with vomit around the mouth. Patient was admitted to emergency, treated with a 'variety of drugs' and diagnosed with baclofen toxicity. *Case 5:* 30-year-old patient found at home unresponsive, twitchy and frothy salivation at the lips. Diazepam relieved the twitching and agitation briefly. Treated for combined alcohol and benzodiazepine withdrawal, but symptoms of withdrawal persisted. Then treated with a barbiturate which resulted in sedation without respiratory depression. Improved over a 5-day period and was discharged to an inpatient drug unit. *Case 6*: 30-year-old patient underwent detoxification with pellet implanted in the abdomen wall. Discharged and visited by a nurse the following day and given drugs to treat his nausea and vomiting.

Continued

Table 21: *(Continued)*

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events
			On the third day patient's family found him unresponsive. Taken to the emergency department where he was in respiratory distress; diagnosed as having bleeding oesophageal varices and probable aspiration pneumonia. Pellets were removed. Experienced multiple seizures and died of cardiac arrest.
Hoffman *et al.* (1998) *Quasi-experimental study*	**Ultra-rapid detoxification under general anaesthesia**		Ultra-rapid detoxification participants (n = 20) compared with five control patients showed elevated blood pressure and lower heart rates under baseline conditions. Ultra-rapid detoxification was associated with increases in respiratory rates and minute ventilation. These reached peak levels approximately 3 hours after the start of naltrexone treatment and remained elevated at end of the treatment. Rapid breathing was seen for up to 24 hours after ultra-rapid detoxification.
Roozen *et al.* (2002) *Case report*	**Rapid naltrexone-accelerated detoxification under sedation –** *level of sedation unclear from report*	Clonidine (0.15 mg qid), lorazepam (2 mg tid), midazolam (15 mg/day), dexamethasone (6 mg, day 1 only), ondansetron (8 mg tid).	37-year-old male, opioid dependent for 20 years and currently maintained on methadone (40 mg/day): Adjunct medications failed to ameliorate diarrhoea and vomiting – admitted to intensive care after

		36 hours of detoxification. On arrival, he was drowsy, his skin was cold and extremities cyanotic. Appeared severely dehydrated and tests indicated acute renal insufficiency. After admission, the service user was rehydrated rapidly. Diarrhoea lasted for several days; a full recovery was made after 2 weeks.
Shreeram *et al.* (2001) *Case report*	**Ultra-rapid detoxification**	A 45-year-old woman taking 100 mg/day methadone and 4 mg/day alprazolam daily (advised to stop alprazolam prior to detoxification): 12 days prior to detoxification, toxicology was positive for methadone and benzodiazepine. Discontinued methadone, but this was still present on screen day before detoxification. Detoxification was initiated and included benzodiazepine substitution. During extubation and over the next few hours the service user was agitated despite being fully orientated. After detoxification, she ingested alprazolam, not provided by clinicians, which she had taken for anxiety. Reported feeling as though previous hours had been a 'bad trip', and believed staff had been trying to kill her. Also reported auditory hallucinations. Symptoms cleared within 24 hours. *Comment: The combination of alprazolam and methadone may be responsible.*

Ultra-rapid detoxification under general anaesthesia
This is associated with a substantially increased risk of serious adverse events, including complications associated with the anaesthesia (such as aspiration pneumonia, delirium and fever), above what would normally be expected in conventional opioid detoxification under minimal sedation. In addition, the polypharmacy of adjunct medications is likely to carry inherent risks. Although the evidence suggests that ultra-rapid detoxification is a very effective way of initiating individuals onto naltrexone maintenance (compared with detoxification with clonidine) and that it may have better abstinence outcomes at 3- to 6-month follow-up, these benefits are outweighed by the considerable risks.

6.6 CLINICAL PRACTICE RECOMMENDATIONS

6.6.1 Accelerated detoxification

6.6.1.1 Ultra-rapid and rapid detoxification using precipitated withdrawal should not be routinely offered. This is because of the complex adjunctive medication and the high level of nursing and medical supervision required.

6.6.1.2 Ultra-rapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death.

6.6.1.3 Rapid detoxification should only be considered for people who specifically request it, clearly understand the associated risks and are able to manage the adjunctive medication. In these circumstances, healthcare professionals should ensure during detoxification that:

- the service user is able to respond to verbal stimulation and maintain a patent airway
- adequate medical and nursing support is available to regularly monitor the service user's level of sedation and vital signs
- staff have the competence to support airways.

6.2.1.4 Accelerated detoxification, using opioid antagonists at lower doses to shorten detoxification, should not be routinely offered. This is because of the increased severity of withdrawal symptoms and the risks associated with the increased use of adjunctive medications.

6.7 PHYSICAL AND COMPLEMENTARY INTERVENTIONS DURING DETOXIFICATION

It is acknowledged that many complementary interventions are offered to individuals with opioid dependence as well as for alcohol or other drug misuse. In this review, the focus was on their use specifically during or for detoxification; their role in other stages of dependency or treatment, such as initiation or maintenance of substitute medication, was not investigated.

A search for RCTs and observational studies for a number of physical and complementary interventions was conducted. Two RCTs, one of acupuncture alone versus placebo (Washburn *et al.*, 1993) and one of acupuncture as an adjunct to tapered methadone (Zeng *et al.*, 2005), met the eligibility criteria, providing data on 170 participants. In addition, one systematic review (Jordan, 2006) covered reviews and clinical trials of acupuncture published between 1973 and 2006. No other suitable/appropriate studies for review were found on any other physical or complementary intervention.

6.7.1 Acupuncture

Acupuncture is a traditional form of Chinese medicine that has been practised for over 3,000 years (Jordan, 2006). It involves inserting fine needles at selected points on the skin to balance the body's energy (chi), with the aim of treating and preventing disease. The review concluded that, despite there being some evidence potentially supporting the use of acupuncture in opioid detoxification, this was mostly derived from trials with poor methodological quality (that is, they were not randomised, not controlled and/or had small sample sizes). In addition, it was not possible to detach possible positive effects of acupuncture from those of other treatments being delivered concurrently. The review found no evidence to support acupuncture as a stand-alone treatment option for opioid dependence (Jordan, 2006).

Further trials, in addition to Jordan's review, were also identified. Zeng and colleagues (2005) randomised participants undergoing a 10-day methadone taper into an acupuncture group (n = 35) and a methadone-only control group (n = 35). The acupuncture group reported significantly lower peak withdrawal severity (SMD = −0.75, 95% CI = −1.29, −0.21) and were also more likely to complete detoxification, with a trend towards significance (RR = 1.19, 95% CI, 0.95 to 1.50), in comparison with controls. However, the lack of an attentional control in the methadone-only group may partly account for the apparent relative efficacy of acupuncture.

Washburn and colleagues (1993) randomised participants to receive detoxification by acupuncture alone (n = 55) or sham acupuncture (n = 45) over 21 days. Although the acupuncture group spent longer time in treatment (acupuncture median = 2 days, sham acupuncture median = 1 days), attrition was extremely high in both groups, with very few completing the 21-day detoxification, suggesting little benefit for acupuncture detoxification.

Clinical summary

In summary, there is a lack of trials assessing the efficacy of acupuncture during detoxification either alone or as an adjunct to other treatments. Therefore there is no established evidence base to support this as an effective method of detoxification.

7. PSYCHOSOCIAL INTERVENTIONS IN OPIOID DETOXIFICATION

7.1 INTRODUCTION

Although detoxification from opioids in NHS settings is generally focussed on pharmacological withdrawal, many detoxification programmes, particularly in specialist units, also include an adjunctive psychosocial component (Day *et al.*, 2005). Recent consensus guidance in the UK (Specialist Clinical Addiction Network [SCAN], 2006) and in the USA (Center for Substance Abuse Treatment [CSAT], 2006) suggests that attempts to treat opioid dependence by means of pharmacological detoxification alone have been shown to have high rates of relapse to dependent use. An obvious consequence of a 'failed' detoxification treatment is the possibility of engendering pessimism in treatment staff and service users alike. The consequence for some service users, particularly those more vulnerable to expectations of failure, might be a further lowering in self-efficacy and the strengthening of beliefs about the inevitability of continued drug dependence. If treatment outcomes can be enhanced through the quality of the therapeutic environment, the availability of adjunctive psychosocial interventions and consequently improved interactions with staff, this pessimism can be effectively challenged.

It has also been argued that detoxification should only be encouraged as the first step in a longer treatment process, and needs to be integrated with relapse prevention or rehabilitation programmes (SCAN, 2006; CSAT, 2006). Detoxification may therefore present a real opportunity to intervene and encourage service users to make changes in the direction of health and recovery. Hence, a primary goal of the detoxification staff should be to build a therapeutic alliance and motivate the service user to enter longer-term treatment for his or her drug misuse. This process should begin even as the service user is being medically stabilised (Onken *et al.*, 1997).

There is good evidence (Roth & Fonagy, 2004) that the quality of the therapeutic alliance established between staff and service user can significantly affect the treatment outcome in a diverse range of disorders. The therapeutic alliance refers to the quality of the relationship between a service user and a care provider. In addition, 'readiness to change' may predict a positive therapeutic alliance (Connors *et al.*, 2000) and there is some evidence to suggest that a positive alliance is associated with a positive outcome in those who are dependent on alcohol or involved in methadone maintenance (Connors *et al.*, 1997). Encouraging engagement with a social support network is also important, as it may be a factor in determining whether the service user stays in treatment (Perez de los Cobos *et al.*, 1997).

It is often argued that psychosocial interventions are an important element of detoxification programmes (Wanigaratne *et al.*, 2005; NTA, 2005c; CSAT, 2006). The aim of these interventions include: supporting retention in treatment for a period long

enough to complete detoxification; providing an opportunity to learn about how to reduce the risk of relapse; and addressing the psychological, social and relationship problems that may have initiated or be maintaining drug use. This is supported by recent cohort study evidence which suggests that service users who remain in contact after detoxification have reduced overdose mortality rates (Davoli *et al.*, in press).

The purpose of this chapter is to review the efficacy of adjunctive psychosocial interventions. Specifically, the chapter aims to find out whether for people who are opioid dependent, psychosocial interventions in combination with detoxification compared with detoxification alone are associated with increased levels of abstinence, completion of treatment and improvements in secondary outcomes. Evidence for the efficacy of these interventions during detoxification is relatively sparse (see Section 7.6). There is more evidence for the efficacy of these psychosocial interventions alone and in combination with opioid agonist maintenance treatment for the treatment of drug misuse (NCCMH, 2008). The abstinence-oriented 12-steps and related self-help approaches, which were assessed by NICE (2007), may have an important role in supporting those undergoing opioid detoxification and pursuing abstinence.

7.1.1 Clinical practice recommendation

7.1.1.1 Service users considering opioid detoxification should be provided with information about self-help groups (such as 12-step groups) and support groups (such as the Alliance); staff should consider facilitating engagement with such services.

7.2 CURRENT PRACTICE

Currently a range of formal psychosocial interventions are available in NHS programmes and include motivational enhancement, CBT, coping skills training, relapse prevention, counselling/supportive-expressive psychotherapy and 12-step approaches (Wanigaratne *et al.*, 2005). However, the relative extent or distribution of these interventions is not well understood and the major provision of psychosocial interventions in the UK consists of keyworking from staff in specialist drug services. This typically includes: assessing need (and risk); establishing and sustaining a therapeutic relationship; identifying treatment goals; implementing and evaluating a treatment plan; liaising and collaborating with other care providers; and aiming to engage and retain the client in treatment and to support the treatment plan (for example, using drug diaries and motivational interviewing skills) in the absence of delivering a complete episode of formal psychological therapy. Contact with service users varies but for those in maintenance treatment, typically this would be fortnightly. In contrast, standard care in the US, at least as described in most of the US studies on detoxification (where it is often referred to as 'drug counselling'), will involve a more frequent level of contact, with formal psychological treatments provided much more often.

7.3 DEFINITIONS

Psychosocial intervention

The term psychosocial intervention is defined here as any formal structured psychological or social intervention with a clearly defined treatment plan and goals, as opposed to advice and information, drop-in support or informal keyworking (NTA, 2005c). Interventions that aim to address a person who misuses drugs and has comorbid mental health problems are outside the scope of the guideline and therefore will not be reviewed in this chapter.

Contingency management

Contingency management provides a system of reinforcers or incentives designed to make continual drug use less attractive and abstinence more attractive (Griffith *et al.*, 2000). There are four primary methods of providing incentives:

- Voucher-based reinforcement: people who misuse drugs receive vouchers with various monetary values (usually increasing in value after successive periods of abstinence) for performing the target behaviour, for example, providing biological samples (usually urine) that are negative for the tested drugs or compliance with particular interventions. These vouchers are withheld when the target behaviour is not performed, for example, the biological sample indicates recent drug use. Once earned, vouchers are exchanged for goods or services that are compatible with a drug-free lifestyle.
- Cash: people who misuse drugs receive cash (usually of a relatively low value, for example, £1.50–£10) for performing the target behaviour, such as submitting a urine sample negative for drugs or compliance with particular interventions. Cash incentives are withheld when the target behaviour is not performed.
- Clinic privileges: participants receive clinic privileges for performing the target behaviour, for example, providing a negative biological sample. But these privileges are withheld when the target behaviour is not performed. An example of a clinic privilege is a take-home methadone dose (for example, Stitzer *et al.*, 1992).
- Prize-based reinforcement: participants receive draws, often from a number of slips of paper kept in a fishbowl, for performing the target behaviour, for example, providing a negative biological specimen. Provision of a specimen indicating recent drug use results in the withholding of draws. Each draw has a chance of winning a 'prize', the value of which varies. Typically, about half of the draws say 'Good job!' The other half contain prizes, which may range in value from £1–£100 (Prendergast *et al.*, 2006).

Community reinforcement approach

In community reinforcement, emphasis is placed on environmental contingencies in aspects of life such as work, recreation, family involvement, and so on, to promote a lifestyle that is more rewarding than drug misuse (Roozen *et al.*, 2004). In almost all studies, the community reinforcement approach for people who misuse drugs is conducted in combination with contingency management.

Family interventions
Family interventions are psychological interventions derived from a model of the interactional processes in families. Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of drug misuse. Additionally, the aim is to change the nature of the interactions so that they may develop relationships that are more supportive and have less conflict (NICE, 2004).

Social network interventions
Professionals seek to promote change by helping the person who misuses drugs to engage with a close network of family members or friends who provide positive social support for attempting or maintaining abstinence (Copello *et al.*, 2005).

Individual drug counselling
This is the assessment of an individual's needs, provision of information and referral to services to meet these needs (including psychosocial interventions, methadone and residential rehabilitation). No attempt is made to engage in any specific formal psychological intervention. Sessions are normally weekly and last 15–20 minutes (Rawson *et al.*, 1983). This to some extent resembles keyworking as used in the UK drug treatment field.

Interpersonal therapy
IPT is a discrete, time-limited, structured psychological intervention, originally developed for the treatment of depression, which focuses on interpersonal issues and where therapist and service user: a) work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current drug misuse, feelings states and/or problems; and b) seek to reduce drug misuse problems by learning to cope with or resolve interpersonal problem areas (Weissman *et al.*, 2000).

Standard cognitive behavioural therapy
Standard CBT is a discrete, time-limited, structured psychological intervention, derived from a cognitive model of drug misuse (Beck *et al.*, 1993). There is an emphasis on identifying and modifying irrational thoughts, managing negative mood and intervening after a lapse to prevent a full-blown relapse (Maude-Griffin, 1998).

Relapse-prevention cognitive behavioural therapy
This differs from standard CBT in the emphasis on training people who misuse drugs to develop skills to identify situations or states where they are most vulnerable to drug use, to avoid high-risk situations, and to use a range of cognitive and behavioural strategies to cope effectively with these situations (Carroll & Onken, 2005).

Short-term psychodynamic interventions
Short-term psychodynamic interventions are derived from a psychodynamic/ psychoanalytic model in which: a) therapist and service user explore and gain insight into conflicts and how these are represented in current situations and relationships, including the therapy relationship; b) service users are given an opportunity to explore feelings and

conscious and unconscious conflicts originating in the past, with the technical focus on interpreting and working through conflicts; c) therapy is non-directive and service users are not taught specific skills such as thought monitoring, re-evaluation or problem solving. Treatment typically consists of 16–30 sessions (Leichsenring *et al.*, 2004).

7.4 OUTCOMES

The two main outcomes reported in studies of detoxification are abstinence and completion. The most important outcome in a detoxification study is abstinence, as that is the goal of the treatment. However, completion was also considered an important measure of detoxification success.

Although studies were examined for follow-up, most studies only provided data up to the end of treatment. Therefore it is difficult to assess the longer-term impact of these interventions.

All studies were examined for reported harms, which included the severity of withdrawal symptoms, side effects of the drugs used and other physical harms to the services users. However, such data is rarely reported in any of the included trials.

Abstinence

Abstinence is here referred to as evidence (usually measured by urinalysis) of drug use at a particular point in time, usually at the end of treatment, although it can also be measured at a follow-up period after treatment.

Completion of treatment

Completion has typically been defined as being retained in treatment up to the final day of its planned duration, ingestion of the final dose of study medication or reaching the point of zero dose of study medication.

7.5 DATABASES SEARCHED AND INCLUSION/EXCLUSION CRITERIA

Information about the databases searched and the inclusion/exclusion criteria used for this section of the guideline can be found in Table 22.

7.6 STUDIES CONSIDERED[7]

The review team conducted a new systematic search for RCTs that assessed the efficacy of psychosocial interventions in combination with detoxification. Only studies where psychosocial interventions were part of a larger integrated programme of detoxification were included.

[7]Here, and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

Table 22: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological interventions

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents December 2005–January 2007
Study design	RCT
Patient population	Opioid dependent
Interventions	Detoxification treatments: methadone, buprenorphine, adrenergic agonists; psychosocial treatments: relapse-prevention CBT, standard CBT, contingency management, community reinforcement approach, family interventions, social network interventions, interpersonal therapy, short-term psychodynamic interventions, individual drug counselling
Outcomes	Abstinence, treatment completion, severity of withdrawal

In the review of contingency management in combination with detoxification, six trials (BICKEL1997; HALL1979; HIGGINS1984; HIGGINS1986; KATZ2004; MCCAUL1984) met the eligibility criteria set by the GDG, providing data on 417 participants. All trials were published in peer-reviewed journals.

In the review of family interventions, one trial (YANDOLI2002) met the eligibility criteria set by the GDG, providing data on 119 participants. This trial was published in a peer-reviewed journal.

In the review of social network interventions, one trial (GALANTER2004) met the eligibility criteria set by the GDG, providing data on 66 participants. This trial was published in a peer-reviewed journal.

In the review of individual drug counselling, one trial (RAWSON1983) met the eligibility criteria set by the GDG, providing data on 50 participants. This trial was published in a peer-reviewed journal.

Six of the included trials were of methadone detoxification (HALL1979; HIGGINS1984; HIGGINS1986; MCCAUL1984; RAWSON1983; YANDOLI2002) and three trials were of buprenorphine detoxification (BICKEL1997; KATZ2004; GALANTER2004).

In addition, two studies were excluded from the analysis. The most common reason for exclusion was lack of adequate comparison groups (further information about both included and excluded studies can be found in Appendix 15).

Evidence from critical outcomes and overall quality of evidence are presented in Table 23. The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

Table 23: Study information and summary evidence table for trials of opioid detoxification plus psychosocial interventions

	Detoxification plus contingency management versus detoxification plus standard care	**Detoxification plus family interventions versus detoxification plus standard care**	**Detoxification plus social network interventions versus detoxification plus standard care**	**Detoxification plus individual drug counselling versus detoxification plus standard care**
Total no. of trials (total no. of participants)	5 RCTs 1 quasi-randomised (N = 417)	1 RCT (N = 119)	1 RCT (N = 66)	1 RCT (N = 50)
Study ID	BICKEL1997 HALL1979 HIGGINS1984 HIGGINS1986 MCCAUL1984 KATZ2004	YANDOLI2002	GALANTER2004	RAWSON1983
Diagnosis	Opioid dependence	Opioid dependence	Opioid dependence	Opioid dependence
Detoxification regimen and treatment length	**Buprenorphine:** 4 days' detoxification (+ 7 days' clonidine patch post-detoxification) Contingency management: $100 voucher for completion of detoxification (KATZ2004)	**Methadone:** Dose reduced by 5 mg every 2 weeks until zero dose Family interventions: up to 16 sessions, initially every 2 weeks then less frequently (YANDOLI2002)	**Buprenorphine:** 5 weeks' stabilisation, 13 weeks' detoxification Social network interventions: 36 sessions for 30 minutes, 18 weeks (GALANTER2004)	**Methadone:** 3 weeks' detoxification Individual drug counselling: Three sessions for 15–20 minutes, 3 weeks (RAWSON1983)

	1 week stabilisation + additional 7–72 days of stabilisation depending on starting dose/70 kg + detoxification for the remainder of 26 weeks Contingency management: 23 weeks (week 1 and weeks 25–26 did not receive contingency management), vouchers increase in value with continuous periods of abstinence from illicit drugs (BICKEL1997) **Methadone:** 16 days' detoxification Contingency management: five vouchers (between $4 and $10) can be earned during detoxification for abstinence from illicit drugs and $15 on completion of detoxification (HALL1979)			

Continued

Table 23: (*Continued*)

	Detoxification plus contingency management versus detoxification plus standard care	**Detoxification plus family interventions versus detoxification plus standard care**	**Detoxification plus social network interventions versus detoxification plus standard care**	**Detoxification plus individual drug counselling versus detoxification plus standard care**
	3 weeks' stabilisation, 10 weeks' detoxification Contingency management: weeks 4–11 of detoxification programme, can increase dose by 5–20 mg for abstinence from illicit drugs (HIGGINS1984; HIGGINS1986) 3 weeks' stabilisation, 10 weeks' detoxification Contingency management: weeks 4–13, twice weekly earn $10 voucher for abstinence from illicit drugs (MCCAUL1984)			

Length of follow-up	End of treatment	1 year	End of treatment	6 months
Evidence profile table number (Appendix 17)	Table A17–15	Table A17–16	Table A17–17	Table A17–18
Overall quality of evidence	Moderate	Moderate	Moderate	Low
Abstinence	End of treatment: 31.1% versus 16.6%, RR 1.86 (1.18, 2.16) K = 4, N = 296	12-month follow-up: 14.6% versus 7.5%, RR 1.95 (0.52, 7.27) K = 1, N = 119	End of treatment: 36.4% versus 18.2%, RR 2.00 (0.85, 4.69) K = 1, N = 66	During treatment: 60% versus 52%, RR 1.15 (0.70, 1.89) K = 1, N = 50
Completion of detoxification	61.5% versus 38.3%, RR 1.60 (1.18, 2.16) K = 5, N = 185		72.7% versus 78.8%, RR 0.92 (0.70, 1.21) K = 1, N = 66	16% versus 12% RR 1.33 (0.33, 5.36) K = 1, N = 50

RR >1 favours intervention.

7.7 PSYCHOSOCIAL INTERVENTIONS IN COMBINATION WITH DETOXIFICATION

7.7.1 Psychosocial interventions in combination with detoxification versus detoxification in combination with standard care

Table 23 summarises the study information and evidence from the included studies.

7.8 CLINICAL SUMMARY

Most studies assessing the efficacy of adjunctive psychosocial interventions were focused on contingency management during community detoxification. Provision of contingency management in the included studies usually began after stabilisation had occurred (for example, Higgins *et al.*, 1984; Higgins *et al.*, 1986) and continued throughout the detoxification process up to completion of treatment. Katz and colleagues (2004) only provided an incentive for the completion of treatment; this is mainly due to the short duration of the detoxification (4 days). People receiving contingency management were more likely to be abstinent at the end of treatment and to complete treatment. This effect was found for short-term interventions (for example, 2 weeks) and those of longer duration (for example, 6 months). NICE (2007) has assessed the use of contingency management to maintain abstinence, including for people who were opioid dependent, finding similar benefits as those summarised above and suggesting the use of this intervention after, as well as during, opioid detoxification. In addition, NICE (2007) reviewed studies concerned with the implementation of contingency management in drug treatment services and the frequency of testing. It was concluded that a tapering strategy of biological testing beginning with three tests per week for the first 3 weeks, followed by two tests per week for the next 3 weeks, followed by one test per week for the remaining treatment period was best supported by the available evidence.

The trial of family interventions consisted of 16 sessions over an indefinite period of time beginning once every 2 weeks and then when needed (Yandoli *et al.*, 2002). Abstinence outcomes were reported for 12-month follow-up; participants in the family intervention group were more likely to be abstinent than the control group but the percentage of abstinent participants in both groups was low (family interventions = 14.6%; control = 7.5%), suggesting benefits were minimal.

The trial of social network interventions lasted 36 sessions over a period of 18 weeks (Galanter *et al.*, 2004). People receiving social network interventions were more likely to be abstinent at the end of treatment compared with the control group. However, there were no differences found between the social network interventions and control groups for completion of treatment. This is to some extent explained by the difficulty found by some participants in the social network group establishing a network. Many of these participants dropped out of treatment at an early stage. Further research is required to establish the efficacy of this intervention.

Individual drug counselling was assessed in one study and lasted three sessions during the 3-week detoxification; it was compared with the control condition, which

made no attempt to engage participants in additional psychosocial interventions (Rawson *et al.*, 1983). The adjunctive provision of individual drug counselling was not associated with improved abstinence or compliance when compared with control, therefore suggesting no additional benefit of this intervention to detoxification outcomes.

7.9 LITERATURE REVIEW OF HEALTH ECONOMICS EVIDENCE

The systematic literature review identified one study that examined the cost effectiveness of contingency management in methadone detoxification (Hartz *et al.*, 1999). Full references, characteristics and results of the study included in the economic review are presented in the form of evidence tables in Appendix 14.

Hartz and colleagues (1999) examined the cost effectiveness of contingency management in a 180-day methadone detoxification study conducted in the US. People dependent on opioids (N = 102) received either detoxification enhanced with contingency management or the same treatment without contingency management. All participants were stabilised to a daily dose of 80 mg of methadone for the first 4 months, followed by a 2-month taper. When methadone doses were fully stabilised, and before initiation of methadone tapering, those in the enhanced treatment were more likely to provide continuously drug-free samples than those in the control group. The incremental cost-effectiveness ratio (ICER) indicated that an additional 1% of participants were continuously substance-free during month 4 for every $17.27 treatment expenditure increase. A cost-benefit analysis estimated that for every additional dollar spent on treatment, a $4.87 healthcare cost offset was realised. However, both of these differences described in the study were not statistically significant owing to small sample size and considerable variation in outcomes in each arm of the trial.

Another finding of the study was that participants receiving treatment enhanced with contingency management incurred moderate healthcare costs compared with control participants, who were more likely to utilise either minimum services or very high-cost services. A possible explanation is that people treated with contingency management tended to seek more regular medical care, whereas people in the control group possibly neglected their health and avoided treatment unless urgent.

7.10 ECONOMIC MODELLING

A decision analytic model was developed to assess the cost effectiveness of contingency management versus standard care for people who misuse opioids receiving detoxification treatment in the UK. Contingency management involved regular contact with a case worker over 13 weeks, combined with reinforcement in the form of vouchers exchangeable for retail goods and services awarded to the service user when weekly abstinence from opioids was achieved. Standard care consisted of less regular contact with a case-worker over the 13-week period. The time horizon of the analysis was 26 weeks. Detoxification lasted for 13 weeks and from that point until the 26th week people misusing drugs in both arms of the model were assumed to receive standard care.

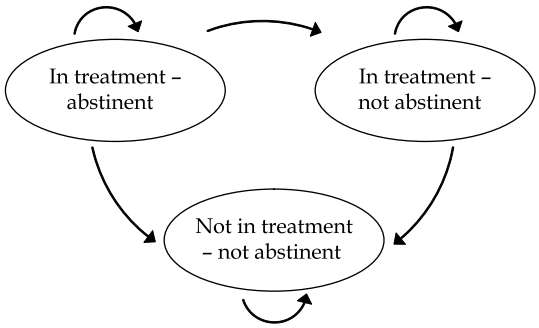
7.10.1 Economic model structure

The economic model consisted of three health states:

- in treatment and abstinent
- in treatment and not abstinent
- not in treatment and not abstinent.

The model was run in weekly cycles. According to the model structure, hypothetical cohorts of the study population received the interventions under assessment and were followed for 26 weeks. People retained in treatment were either abstinent or not abstinent. People who dropped out or were lost at follow-up were assumed to misuse illicit opioids and to remain non-abstinent thereafter. Once people were found not abstinent, they could not move back to the abstinent state. A schematic diagram of the Markov model is presented in Figure 3.

Figure 3: Schematic structure of the economic model



7.10.2 Costs and health benefits included in the analysis

The economic analysis adopted the perspective of the NHS and personal social services (PSS). Costs included intervention costs and additional healthcare costs such as those associated with A&E attendances, primary and secondary care for physical health problems, as well as mental healthcare. A further non-reference case analysis was undertaken. This analysis, besides NHS/PSS costs, included criminal justice system and crime victim costs, because the economic impact of drug misuse on the criminal justice system and victims of crime was judged to be significant. The measure of health benefit used in the analysis was the quality adjusted life year (QALY).

7.10.3 Effectiveness data used in the model

Effectiveness data for the 13-week intervention period were derived from meta-analyses of RCTs that compared the effectiveness of contingency management and standard care in illicit opioid users receiving methadone detoxification treatment. Data from

studies that reported percentages of service users receiving methadone detoxification remaining abstinent from opioids at certain points after initiation of treatment were utilised. Follow-up data on abstinence rates after 13 weeks of contingency management or standard care and up to 6 months were not available in the literature for people having undergone detoxification. Nevertheless, data on abstinent rates at the end of intervention and at 6-months were reported in RCTs comparing contingency management versus standard care in people receiving methadone maintenance treatment (Epstein *et al.*, 2003, Petry *et al.*, 2005, Rawson *et al.*, 2002, Silverman *et al.*, 1998). Following meta-analysis of these data, weekly rates of failing to remain abstinent between completion of the intervention (either contingency management or standard care) and 6 months were estimated and subsequently utilised in the economic model in order to estimate the levels of abstinence of opioid users under detoxification with or without contingency management up to 6 months. Table 24 presents the effectiveness data used in the economic analysis and the clinical studies from which these were derived. Details of the clinical studies on contingency management in people receiving detoxification treatment used in the economic analysis are provided in Appendix 15.

Data on retention in treatment used in the economic analysis for the 13-week intervention period were derived from the meta-analysis of RCTs comparing the effectiveness of contingency management and standard care in illicit opioid users receiving methadone detoxification treatment.

Follow-up data on retention in treatment (that is, in regular contact with health services) at completion of the intervention and at 6 months were taken from meta-analyses of RCTs comparing contingency management versus standard care in illicit opioid users receiving methadone maintenance treatment (Epstein *et al.*, 2003; Petry *et al.*, 2005; Petry & Martin, 2002). These data were used to estimate weekly drop-out rates between completion of the intervention and at 6 months. Table 25 provides the data on the retention rates used in the economic analysis and the clinical studies from which these were derived.

Table 24: Data on abstinence rates utilised in the economic model and weekly rates of failing to remain abstinent at follow-up

Data derived from meta-analysis			**Studies included**
A. Percentage of users abstinent at 1 week of treatment (guideline meta-analysis)			
Intervention	*Mean*	*95% CI*	KATZ2004
CM	31.19%	22.85 to 40.88	
Standard care	17.65%	11.07 to 26.73	
RR	1.77	1.07 to 2.92 (fixed effects model)	

Continued

Table 24: (*Continued*)

B. Percentage of users abstinent at 2 weeks of treatment (guideline meta-analysis)			
Intervention	*Mean*	*95% CI*	HALL1979
CM	62.50%	45.81 to 76.83	
Standard care	51.22%	35.37 to 66.85	
RR	1.22	0.83 to 1.79 (fixed effects model)	
C. Percentage of users abstinent at 13 weeks of treatment (guideline meta-analysis)			
Intervention	*Mean*	*95% CI*	MCCAUL1984 HIGGINS1986
CM	39.13%	20.47 to 61.22	
Standard care	17.39%	5.72 to 39.55	
RR	2.25	1.55 to 3.58 (fixed effects model)	
D. Percentage of users abstinent at completion of intervention (studies on methadone maintenance treatment)			
Intervention	*Mean*	*95% CI*	Epstein *et al.,* 2003 Petry *et al*., 2005 Rawson *et al.,* 2002 Silverman *et al*., 1998
CM	40.88%	32.66 to 49.62	
Standard care	14.07%	8.90 to 21.35	
RR	2.90	1.84 to 4.58 (fixed-effects model)	
E. Percentage of users abstinent at 6 months (studies on methadone maintenance treatment)			
Intervention	*Mean*	*95% CI*	Epstein *et al.*, 2003 Petry *et al.*, 2005 Rawson *et al.*, 2002 Silverman *et al.*, 1998
CM	25.55%	18.66 to 33.84	
Standard care	13.33%	8.30 to 20.51	
RR	1.88	1.15 to 3.05 (fixed-effects model)	

Table 25: Data on retention in treatment utilised in the economic model

Data derived from meta-analysis			**Studies included**
A. Percentage of users remaining in the study at 13 weeks (guideline meta-analysis)			
Intervention	*Mean*	*95% CI*	HIGGINS1984 HIGGINS1986 MCCAUL1984
CM	65.63%	46.78 to 80.83	
Standard care	33.33%	18.55 to 51.89	
RR	1.95	1.95 to 3.34 (fixed effects model)	
B. Retention rates at completion of intervention (studies on methadone maintenance treatment)			
Intervention	*Mean*	*95% CI*	Epstein *et al.*, 2003 Petry *et al.*, 2005 Petry & Martin, 2002
CM	85.85%	77.42 to 91.60	
Standard care	81.65%	72.84 to 88.17	
RR	1.05	0.94 to 1.18	
C. Retention rates at 6-month follow-up (studies on methadone maintenance treatment)			
Intervention	*Mean*	*95% CI*	Epstein *et al.,* 2003 Petry *et al*., 2005 Petry & Martin, 2002
CM	75.47%	65.98 to 83.08	
Standard care	73.39%	63.92 to 81.19	
RR	1.03	0.88 to 1.20	

7.10.4 Cost data

Owing to lack of patient-level cost data, deterministic costing of relevant resources was undertaken (that is, costs were analysed as point estimates). Resource utilisation with respect to the interventions assessed (contingency management and standard care) was estimated by the GDG to reflect UK clinical practice. The estimate was subsequently combined with unit prices to provide the total intervention cost. For each intervention, the GDG estimated the frequency and duration of contacts with case workers and the frequency of urinalysis tests (dipsticks) undertaken for the detection of opioids. The GDG also estimated the average daily dose of methadone administered to the service users over the detoxification period. People in the contingency management arm were assumed to receive a £3 voucher for each week they remained abstinent from opioids during the first 6 weeks of the intervention, and a £5 voucher for each week of abstinence during the next 7 weeks of the intervention.

Case-worker unit costs (assumed to be equivalent to those of community nurses paid according to Band 6) were taken from Curtis and Netten (2006). The price of urine dipsticks was determined by personal communication with a pharmacist. Methadone unit costs were taken from *BNF 53* (March 2007). Resource utilisation estimates and unit costs associated with contingency management and standard care are presented in Table 26.

Table 26: Resource utilisation estimates and unit costs associated with contingency management and standard care

Resource utilisation (GDG opinion)	
CM Weeks 1–3: three contacts per week with a case worker, lasting 30 minutes each Weeks 4–6: two contacts per week with a case worker, lasting 30 minutes each Weeks 7–13: one contact per week with a case worker, lasting 30 minutes each Weeks 14–26: one contact per fortnight with a case worker, lasting 20 minutes each Plus urinalysis (dipstick) Weeks 1–13: once per week Weeks 14–26: once per fortnight Plus reinforcers: £3 voucher per week of abstinence during the first 6 weeks in treatment £5 voucher per week of abstinence during the following 7 weeks in treatment ***Standard care*** Weeks 1–13: one contact per week with a case worker, lasting 20 minutes Weeks 13–26: one contact per fortnight with a case worker, lasting 20 minutes each Plus: urinalysis (dipstick) Weeks 1–13: once per week Weeks 14–26: once per fortnight ***Methadone detoxification*** Weeks 1–3: 30 mg daily Weeks 4–10: 5 mg reduction in dosage per day (week 10: 0 mg) Weeks 10–13: placebo Weeks 14–26: none	
Unit costs	**Source**
Case worker per hour of clinic contact: £53	Curtis & Netten (2006); cost of community nurse (Band 6); qualification costs excluded
Urinalysis (dipstick): £1.50	Personal communication with a pharmacist
Methadone oral solution 1 mg/ml: £0.0135/mg	*BNF 53*

Further healthcare costs, including costs associated with A&E attendances, GP visits and inpatient care for physical health problems, as well as inpatient and outpatient mental healthcare, were based on resource use data derived from the NTORS study (Gossop *et al.*, 1998). Using these data, Godfrey and colleagues (2002) estimated the annual healthcare costs incurred by Class A problem drug users in England and Wales, excluding treatment for dependence. Costs were reported separately for drug users not in treatment for dependence, for those in treatment for less than a year, and for those in treatment for more than a year. Costs relating to the first two categories of users were utilised in the economic analysis. Table 27 provides healthcare resource use estimates and respective costs incurred by drug users in England and Wales as reported in Godfrey and colleagues (2002).

From Table 27 it can be seen that healthcare costs are higher for users in treatment than for those not in treatment. This finding suggests that increasing the number of users in treatment may result in an increase in healthcare costs in the short term. In addition, healthcare costs estimated by Godfrey and colleagues (2002) were not

Table 27: Annual healthcare resource use and costs incurred by Class A problem drug users in England and Wales (Godfrey *et al.,* 2002; 2000 prices; costs in brackets refer to lowest and highest estimates)

A. Drug users not in treatment		
Type of healthcare	*Annual resource use per user*	*Annual cost per user*
Primary care	3.6 GP visits	£65
A&E	0.7 episodes	£197
Inpatient care	1.75 days	£390
Community mental health	1.3 visits	£65
Inpatient mental health	1.5 days	£216
Total		**£933 (£780–£1,400)**
B. Drug users in treatment for less than a year		
Type of health care	*Annual resource use per user*	*Annual cost per user*
Primary care	5.6 GP visits	£101
A&E	0.8 episodes	£226
Inpatient care	2.8 days	£624
Community mental health	0.8 visits	£40
Inpatient mental health	0.4 days	£58
Total		**£1,049 (£873–£1,572)**

adjusted to take into account the impact of current drug use on future healthcare demands. As a consequence, potential future costs from infectious disease risks among drug users have not been included in the above estimates of healthcare costs and, hence, in the economic analysis undertaken for this guideline.

Godfrey and colleagues (2002) did not report data on PSS costs associated with drug misuse; for this reason, such costs have been assumed to be negligible in the economic analysis. Criminal justice system and crime victim costs, which were included in the non-reference case analysis, were available in Godfrey and colleagues (2002). Criminal justice system costs included costs associated with drug arrests, arrests for acquisitive crimes, stays in police custody, appearances in court, and stays in prison. Crime victim costs referred to material or physical damage and loss, expenditures taken in anticipation of crime, and the wider fear of criminal elements. Table 28 provides estimates of crime-related costs for people who misuse drugs not in treatment and for those in treatment for less than a year, as reported in Godfrey and colleagues (2002).

It should be noted that the amount of healthcare costs and crime-related costs incurred by people who misuse drug as reported in Godfrey and colleagues (2002) exclusively depended on whether they were engaged in treatment or not; the impact of effectiveness of treatment (in terms of achieving abstinence from drug misuse) on these costs was not discussed in the study; therefore, the economic analysis undertaken for this guideline has not differentiated between abstinent users and non-abstinent users in treatment at estimation of costs.

Healthcare costs were adjusted to 2006 prices using the hospital and community health services (HCHS) pay and price inflation rates (Curtis & Netten, 2006). The inflation rate for 2005/2006 was estimated using the average value of the HCHS pay and price inflation rates of the previous 3 years. Crime-related costs were adjusted to 2006 prices using the Retail Prices Index (Office for National Statistics, 2007).

Table 28: Annual criminal justice system and crime victim costs incurred by Class A problem drug users in England and Wales (Godfrey *et al.*, 2002; 2000 prices; costs in brackets refer to lowest and highest estimates)

A. Drug users not in treatment	
Criminal justice system cost	£7,037 (£5,864–£10,556)
Victim costs of crime	£30,827 (£25,691–£46,242)
TOTAL	**£37,864 (£31,555–£56,798)**
B. Drug users in treatment for less than a year	
Criminal justice system cost	£8,397 (£6,997–£12,582)
Victim costs of crime	£8,893 (£7,417–£13,357)
Total	**£17,290 (£14,414–£25,939)**

7.10.5 Utility data

Utility values required for the estimation of QALYs were derived from data reported in two recent NHS Health Technology Assessments of methadone and buprenorphine, and of oral naltrexone for the management of opioid-dependent drug users (Connock *et al.*, 2007, Adi *et al.*, 2007). Utility data in these studies were obtained by a panel of members of the public, co-ordinated by the Peninsula Technology Assessment Group (PenTAG). The panel made valuations of given health states via the Value of Health Panel website using the standard gamble technique. The utility values resulting from this exercise, which were used in the economic analysis performed in this guideline, are presented in Table 29.

Table 29: Utility values used in the economic analysis (Connock *et al.*, 2007, Adi *et al.*, 2007)

Health state	Utility value (range)
In treatment–drugs free	0.8673 (0.525–1)
In treatment–drugs reduction	Injectors: 0.6332 (0.275–0.935)
Not in treatment–drug misusers	Injectors: 0.5880 (0.125–0.960)

7.10.6 Sensitivity analysis

In addition to the base-case analysis, which utilised the most accurate data available, a sensitivity analysis was undertaken to investigate the robustness of the results under the uncertainty characterising the model input parameters. Selected parameters were varied over a range of values and the impact of these variations on the results was explored. The following scenarios were tested in sensitivity analysis:

- Change in the RRs of the percentage abstinence during treatment or at follow-up of service users receiving contingency management versus standard care. The 95% CIs of RRs calculated in the guideline meta-analyses, as shown in Table 24, were used. Two scenarios examined the simultaneous use of the lower 95% CIs and the upper 95% CIs of all estimated RRs, respectively.
- Changes in the total value of vouchers received by abstinent service users undergoing contingency management. A 100% increase and a 50% decrease were examined.
- Changes in the additional (that is, besides intervention costs) healthcare and crime-related costs. Lowest and highest estimates reported in Godfrey and colleagues (2002), as shown in Table 27 and Table 28, were used.
- Exclusion of crime victim costs from the non-reference case analysis, as crime victim costs differed greatly between users in treatment (£8,893) and users not in treatment (£30,827) in Godfrey and colleagues (2002).

7.10.7 Results

Base-case analysis

Contingency management was cost effective over 26 weeks. The ICER of contingency management versus standard care was £15,753/QALY from an NHS/PSS perspective. From a wider perspective including criminal justice system and crime victim costs, detoxification with contingency management dominated standard detoxification; it was more effective and cheaper at the same time. Full results of the analysis are provided in Table 30.

Table 30: Results of the economic analysis: total average costs and QALYs per user under contingency management or standard care, over a year of follow-up

Intervention	Average total cost (NHS/PSS)	Average total cost (NHS/PSS plus crime-related)	Average number of QALYs	ICER of contingency management versus standard care
Contingency management	£1,216	£14,910	0.34	£15,700/QALY (NHS/PSS) Contingency management dominates (NHS/PSS plus crime-related)
Standard care	£807	£17,654	0.32	
Difference	£408[8]	£−2,744	0.03	

Sensitivity analysis

From a NHS/PSS perspective, results were sensitive to changes in the RRs of the percentage abstinence achieved by users receiving contingency management versus standard care. When the lower 95% CIs of all estimated RRs were used, the ICER of contingency management versus standard care became £22,225/QALY. It must be noted, though, that the base-case results were less sensitive under changes in the RRs of abstinence rates referring to the 13-week intervention period only (that is, when RRs of abstinence rates achieved at follow-up remained intact). In this case, the ICER of contingency management versus standard care was £20,732/QALY, which is very close to the cost-effectiveness threshold of £20,000/QALY set by NICE (NICE, 2005).

The ICER was robust in changes in the value of reinforcing vouchers, as well as in the use of lowest and highest estimates of healthcare costs reported in Godfrey and colleagues (2002).

When a wider perspective that included crime-related costs was considered (non-reference case analysis), contingency management was the dominant option under all scenarios explored.

Full results of the one-way sensitivity analysis are provided in Table 31.

[8]The figures in the model were calculated using many decimal places and some figures are rounded.

Table 31: Results of sensitivity analysis

Input parameter varied	Results – NHS/PSS analysis	Results – non-reference case analysis
RRs of abstinence		
Lower 95% CIs	£26,623/QALY	Contingency management dominates standard care
Upper 95% CIs	£9,347/QALY	Contingency management dominates standard care
Costs of vouchers		
100% increase	£16,465/QALY	Contingency management dominates standard care
50% decrease	£15,317/QALY	Contingency management dominates standard care
Additional healthcare and crime-related costs		
Lowest estimates	£15,557/QALY	Contingency management dominates standard care
Highest estimates	£16,070/QALY	Contingency management dominates standard care
Exclusion of crime victim costs	N/A	Contingency management dominates standard care

In addition to one-way sensitivity analyses, a threshold analysis was undertaken in order to explore the impact of using follow-up data on abstinence and retention rates from RCTs assessing contingency management in users receiving methadone maintenance treatment rather than detoxification treatment, owing to a lack of more relevant data. For this purpose, the estimated relative risk of failing to remain abstinent of contingency management versus standard care at follow-up was varied. This RR equalled 8.46 in the base-case analysis; threshold analysis showed that it had to reach 37.17 in order for the ICER of contingency management versus standard care to exceed the £20,000/QALY set threshold. Likewise, the estimated relative risk of dropping out at follow-up of contingency management versus standard care was 1.21; threshold analysis revealed that this figure had to rise to 12.19 in order for the ICER of contingency management versus standard care to exceed the £20,000/QALY threshold. It is unlikely that both RRs (either of failing to remain abstinent or of dropping out of treatment at follow-up), are substantially different between service users receiving detoxification treatment and those receiving methadone maintenance treatment, and it is highly unlikely that they approximate to the cut-off points identified in threshold analyses; therefore, use of follow-up data from the methadone maintenance treatment population seemed to be a safe assumption.

Limitations of the economic analysis and overall conclusions

The results of the analysis are subject to various limitations. Since follow-up data on abstinence and retention rates were not available for service users undergoing

detoxification receiving contingency management or standard care, we used data from service users receiving methadone maintenance treatment, contingency management or standard care. Threshold analysis showed that it was safe to make such an assumption because the estimated relative risks of contingency management versus standard care in service users receiving methadone maintenance treatment regarding failure to remain abstinent and dropping out of treatment should be substantially increased before contingency management ceased to be a cost-effective option. It is unlikely that these relative risks are so much higher in service users undergoing detoxification compared with those receiving methadone maintenance treatment. It has to be acknowledged, though, that methadone maintenance treatment and detoxification are two interventions with different approaches and aims so the study populations may present differences in terms of abstinence levels and rates of retention in treatment at follow-up. In addition, in order to construct the economic model it was assumed that once service users were found to misuse opioids, they continued misusing opioids and did not achieve abstinence thereafter. This assumption is rather conservative and may not accurately reflect abstinence trends among users over time.

The time horizon of the analysis is very limited (only 6 months) owing to lack of data allowing further extrapolation. Retention and abstinence rates at the end of detoxification and at 6-month follow-up were higher for the contingency management group. So, limiting the time horizon at 6 months may be a conservative approach that underestimates the cost effectiveness of detoxification with contingency management in the long term.

Intervention costs were based on GDG estimates of relevant resource use, owing to lack of research-based data. Other healthcare costs, as well as crime-related costs that were included in the non-reference case analysis, were derived from Godfrey and colleagues (2002), who estimated such costs based on UK resource use data. According to the study, these costs depended exclusively on retention of people who misuse drugs in treatment, and were not affected by levels of abstinence achieved by treatment. This is a rather conservative assumption, at least in the longer term. If remaining in abstinence for longer periods reduces healthcare resource use and costs related to crime, then the cost effectiveness of contingency management is greater than that estimated in this analysis, since contingency management is more effective than standard care in achieving higher rates and longer periods of abstinence.

Long-term healthcare costs incurred by drug misuse, such as costs associated with infectious disease risks among injecting drug misusers, were not considered in the economic analysis, as no data were available in the literature. However, some of these costs have already been taken into account in the estimation of healthcare costs of drug misusers reported by Godfrey and colleagues (2002). Voluntary sector costs, social service costs and productivity losses were not included in the analysis. If all these cost elements are expected to be lower when higher rates of abstinence are achieved, then contingency management is likely to be more cost effective than the findings of the analysis suggest.

Contingency management was shown to be a cost-effective option under most scenarios explored from an NHS/PSS perspective. Results were only sensitive to the uncertainty characterising the effectiveness data on people who misuse drugs under

maintenance methadone treatment at 6-month follow-up. On the other hand, when a wider perspective including criminal justice and crime victim costs was considered, contingency management was cost-effective (dominant option) under all scenarios tested in sensitivity analysis. In conclusion, despite the limitations of the analysis, the results indicate that contingency management is likely to be a cost effective option for users of illicit opioids undergoing methadone detoxification treatment, especially when the wider economic, social and public health consequences of drug misuse are considered.

7.11 CLINICAL PRACTICE RECOMMENDATIONS

7.11.1.1 Contingency management aimed at reducing illicit drug use should be considered both during detoxification and for up to 3–6 months after completion of detoxification.

7.11.1.2 Contingency management during and after detoxification should be based on the following principles.

- The programme should offer incentives (usually vouchers that can be exchanged for goods or services of the service user's choice, or privileges such as take-home methadone doses) contingent on each presentation of a drug-negative test (for example, free from cocaine or non-prescribed opioids).
- If vouchers are used, they should have monetary values that start in the region of £2 and increase with each additional, continuous period of abstinence.
- The frequency of screening should be set at three tests per week for the first 3 weeks, two tests per week for the next 3 weeks, and one per week thereafter until stability is achieved.
- Urinalysis should be the preferred method of testing but oral fluid tests may be considered as an alternative.

7.11.1.3 Staff delivering contingency management programmes should ensure that:

- the target is agreed in collaboration with the service user
- the incentives are provided in a timely and consistent manner
- the service user fully understands the relationship between the treatment goal and the incentive schedule
- the incentive is perceived to be reinforcing and supports a healthy/drug-free lifestyle.

7.11.1.4 Drug services should ensure that as part of the introduction of contingency management, staff are trained and competent in appropriate near-patient testing methods and in the delivery of contingency management.

7.11.1.5 Contingency management should be introduced to drug services in the phased implementation programme led by the National Treatment Agency for Substance Misuse (NTA), in which staff training and the development of service delivery systems are carefully evaluated. The outcome of this evaluation should be used to inform the full-scale implementation of contingency management.

8. SETTINGS FOR OPIOID DETOXIFICATION

8.1 INTRODUCTION

Detoxification from opioids takes place in a variety of settings, including the community, inpatient units, residential units and prisons. Although there are no precise data, it has been estimated that if those taking place in prison are excluded, at least 90% of opioid detoxifications take place in the community, with only a very small number being treated as inpatients. The NDTMS (2003–2004) reports that 3% of all drug service users receive inpatient or residential detoxification, but there is no specific data on community-based detoxification or what proportion were opioid cases (NTA, 2005a). In addition, approximately 56,000 service users currently undergo detoxification in prison every year (DH, 2006). In the past few years, there has been an increasing emphasis on legally sanctioned treatment, which may include detoxification, both under coerced conditions as Drug Rehabilitation Requirements (formerly DTTOs) and under voluntary conditions as the Drug Interventions Programme (DIP).

Inpatient detoxification is expensive to provide and this has led to a reduction in its availability—in some areas of England and Wales provision is almost non-existent despite recommendations that it should be available (NTA, 2002, 2005c). Community-based detoxification is available both through specialist drug services and some primary care services.

Currently, the evidence for the importance of setting in affecting the outcome for detoxification is very sparse, with little research being available to guide clinicians about the service and setting in which users are likely to do well. In addition, for some, such as those in prison, it is helpful to know whether detoxification treatments are likely to be clinically useful, as goals for this group of service users may differ from their counterparts in the community.

Treatment settings in England and Wales

Detoxification in community settings has traditionally divided into specialist and primary-care-based services. Specialist services, often known as community drug teams, are multidisciplinary and are led by an addiction psychiatrist or another addiction specialist and are staffed by professionals from a range of disciplines, including medicine, nursing, psychology and social work, and drug workers (usually graduates with experience and qualifications in treating drug users). Primary care encompasses a range of treatment models, from the GP providing the treatment with no support, to drug workers or nurses working with a GP in a surgery, to services that resemble a community drug team with a doctor from a primary care background providing the leadership.

Another important community setting is the criminal justice treatment service. Service users treated in the DIP will in most cases receive the same treatment in the

community drug team or primary care drug services as non-DIP service users, therefore any differences in outcome would not be attributed to the setting.

Detoxification can take place in inpatient or residential settings. As noted above, inpatient detoxification has a limited availability but involves a medically led multidisciplinary team with a full nursing team. In some areas, the inpatient beds are located on a psychiatric ward with no specialist provision for detoxification. In addition, some voluntary and private residential units also provide medically managed care with high staff levels, including 24-hour nursing and medical cover (SCAN, 2006). Other settings may offer medically monitored detoxification but often lack both 24-hour nursing and medical cover. Although some units in England run by the non-statutory sector provide only detoxification, most are usually rehabilitation centres, where opioid-dependent service users may go for an extended period of psychosocial rehabilitation and are offered detoxification as part of the programme. The whole situation is complicated by the fact that some service users are detoxified on general psychiatric or medical and surgical wards as they are being treated there for other conditions (SCAN, 2006).

With very large numbers of people who misuse opioids receiving treatment in prison each year (DH, 2006), prisons are now recommended to structure their care into an early high-intensity phase similar to the inpatient settings already described, with 24-hour supervision by trained healthcare staff, a second stage of continued enhanced support and, finally, 'outpatient'-type care back in the main prison community. A menu of psychosocial treatment options accompanies the provision of pharmacological treatments for 28 days after reception into prison (Home Office Drug Strategy Directorate, 2006). Prisoners who are opioid dependent can undergo detoxification in any of these stages (DH, 2006). However, caution should be exercised where the necessary stabilisation period and support required for people undergoing detoxification in prison settings may not be possible, in situations such as short prison sentences, a short period of remand and for those in police custody. In such situations, the level of assessment and monitoring for detoxification treatment may be limited due to time constraints and the potential for short notice of release or transfer.

In understanding the evidence for the effectiveness of various detoxification regimens, attention should be given to the content of the intervention and the nature of support that is provided within a community setting, for example, how much individual contact service users have with a worker, whether they are seen in their home, how often they are seen and what services are provided.

Current practice

Service users may wish to become abstinent at any time in a period of treatment, from initial contact with services to many years into their opioid dependence following a long period of maintenance treatment. Accident and emergency departments are often the first point of contact with health services for many people who misuse drugs, who primarily attend for treatment of accidental overdose (Gossop *et al.*, 1995). Although this encounter presents an opportunity to refer drug users to drug

treatment services, or to encourage them to consider addressing their drug misuse, detoxification treatment should not normally be immediately initiated within this setting. The majority of opioid users who want to become abstinent are offered community detoxification as the first-line treatment. In some areas of the country, opioid users currently have a choice between treatments offered by the local community drug service or by their GP, although that option is not always available. There may be considerable variation in the level of support provided during a period of community detoxification.

Inpatient detoxification is usually only offered after community treatment has repeatedly failed (SCAN, 2006). It is often offered before a period of residential rehabilitation, as many programmes require service users to be drug free before entry. It is common practice to offer inpatient detoxification to the service users with the most complex needs (SCAN, 2006). These are usually those with multiple dependencies (for example, benzodiazepines and alcohol), those with dual physical and mental health diagnoses and those who are particularly socially chaotic.

Day and colleagues (2005) conducted a survey on provision of inpatient and residential detoxification. There were an estimated 532 beds available for people detoxifying from drugs in residential rehabilitation units in the UK, with a total of 1,085 admissions per year. There were estimated to be 356 specialist inpatient beds available for drug detoxification, with an estimated 6,829 annual admissions. In addition, there were an estimated 103 beds available in non-specialist psychiatric or medical wards, with a total of 2,077 admissions per year for drug detoxification. This resulted in a combined estimate of 10,711 annual admissions for people who misuse drugs in inpatient and residential treatment (Day *et al.*, 2005).

8.1.1 Clinical practice recommendation

8.1.1.1 Opioid detoxification should not be routinely offered to people:

- with a medical condition needing urgent treatment
- in police custody, or serving a short prison sentence or a short period of remand; consideration should be given to treating opioid withdrawal symptoms with opioid agonist medication
- who have presented to an acute or emergency setting; the primary emergency problem should be addressed and opioid withdrawal symptoms treated, with referral to further drug services as appropriate.

8.2 INPATIENT AND COMMUNITY-BASED SETTINGS

8.2.1 Databases searched and inclusion/exclusion criteria

Information about the databases searched and inclusion/exclusion criteria can be found in Table 32.

Table 32: Databases searched and inclusion/exclusion criteria for clinical effectiveness of inpatient, residential and community detoxification

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005–January 2007
Study design	RCT Observational studies
Patient population	Opioid dependent
Interventions	Detoxification in the following settings: inpatient, community, residential
Outcomes	Abstinence, treatment completion

8.2.2 Studies considered[9]

The review team conducted a new systematic search for RCTs and observational studies that assessed the efficacy of detoxification in inpatient, residential and community-based settings.

In the review comparing inpatient/residential detoxification with community-based detoxification, three trials (DAY2006; GOSSOP1986; WILSON1975) met the eligibility criteria set by the GDG, providing data on 171 participants. Two trials (GOSSOP1986; WILSON1975) were published in peer-reviewed journals and one trial (DAY2006) was unpublished.

In the review comparing specialist inpatient detoxification and generic inpatient detoxification, one trial (Strang *et al.*, 1997b) met the eligibility criteria set by the GDG, providing data on 99 participants. This trial was published in a peer-review journal.

In the review comparing detoxification in a specialist community-based drug clinic and detoxification in a community-based primary care clinic, one trial met the criteria set by the GDG (Gibson *et al.*, 2003), providing data on 115 participants. This trial was published in a peer-reviewed journal.

Evidence from critical outcomes and overall quality of evidence are presented in Table 33. The forest plots and full evidence profiles can be found in Appendix 16 and Appendix 17, respectively.

In addition, two studies were excluded from the analysis. The most common reason for exclusion was lack of adequate comparison groups (further information about both included and excluded studies can be found in Appendix 15).

[9]Here, and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

8.2.3 Inpatient detoxification versus community-based detoxification

Three trials were identified that compared inpatient and community-based detoxification. The two RCTs (DAY2006; WILSON1975) were meta-analysed and summarised below (see Table 33). The third trial, which did not provide separate data for patient preference and randomised samples, was reported separately.

Table 33 shows that participants receiving inpatient detoxification were more likely to complete their detoxification than those receiving this treatment in the community (RR = 1.60; 95% CI, 1.05 to 2.42). However, this should be interpreted with caution as results are more modest (RR = 1.38; 95% CI, 0.79 to 2.42) for the recent UK trial (DAY2006) in comparison with Wilson and colleagues' (1975) earlier US trial (RR = 1.91; 95% CI, 1.03 to 3.55). A number of additional problems with the data from Wilson and colleagues (1975) limit the strength of the conclusions that can be drawn. There is evidence that data from the urine samples were not reliable: a small number of urines were tested in the hospital group, and 42.9% were reported to be contaminated. Therefore comparisons between the two groups on continuing drug use are problematic. Furthermore, the restricted starting dose of methadone (40 mg in the first 24 hours) limits the applicability of this study to current practice, where much higher doses are now recommended (DH, 1999) and may further suggest the lack of applicability of this trial to current UK clinical practice.

A third trial considered in this review (Gossop *et al.*, 1986) was not included in the meta-analysis because randomised and non-randomised data were combined. This trial also compared people receiving inpatient detoxification with those who received community-based detoxification and, consistent with the data above, found statistically significant differences between inpatient and community-based

Table 33: Summary evidence table for inpatient detoxification compared with community-based detoxification

	Inpatient detoxification versus community-based detoxification
Total no. of trials (total no. of participants)	2 RCTs (N = 111)
Study ID	DAY2006 WILSON1975
Length of follow-up	End of treatment
Evidence profile table number (Appendix 17)	Table A17-19
Overall quality of evidence	Low
Completion of detoxification	53% versus 36%, RR 1.60 (1.05 to 2.42) K = 2, N = 111

RR > 1 favours inpatient detoxification.

detoxification. Sixty participants, who were opioid dependent, elected to receive either inpatient or community-based detoxification. Participants were assigned to one of four groups: preferred inpatient, preferred community-based, randomised inpatient and randomised community-based. Forty participants expressed strong preferences and were assigned to the appropriate groups. The remaining 20 subjects were randomly assigned to one of the randomised groups. Differences between inpatient and community-based settings were much more pronounced in this trial compared with the other RCTs (DAY2006; WILSON1975). In total, 81% of the inpatient group were successfully detoxified from opioids compared with 17% in the community-based group (RR = 4.68; 95% CI 2.07 to 10.58).

The main finding of the study was that supervised inpatient detoxification was more successful than the community-based comparison group. However, there are two main problems with this study. Firstly, data comparing outcomes in the community-based and inpatient settings were combined from participants who were assigned by preference and participants who were randomly assigned. There was a strong trend favouring participants in the preferred group (RR = 1.64; 95% CI 0.85 to 3.16). In addition, the level of support and therapy within the inpatient group was significantly higher, although of a shorter duration (21 days), whereas the community-based detoxification programme was for 8 weeks and no support was provided outside the clinic.

The evidence base comparing detoxification in inpatient and community-based settings is limited. There is some evidence suggesting inpatient detoxification is more effective than community-based detoxification. But two of the three trials (WILSON1975; Gossop *et al.*, 1986) had significant methodological limitations that make these findings difficult to interpret.

8.2.4 Specialist inpatient versus generic inpatient

One RCT was identified that compared detoxification in specialist and generalist settings. Strang and colleagues (1997b) compared outcomes from people with opioid dependence receiving detoxification in a specialist drug dependency unit with those on a general psychiatric ward. A total of 186 participants were randomised to the waiting list for treatment in either a drug dependency unit (n = 115) or a general psychiatric ward (n = 71). However, only 69 in the drug dependency unit group and 30 in the general psychiatric ward group remained after the waiting list period to enter inpatient treatment. A total of 75% completed detoxification in the drug dependency unit, compared with 43% in the general psychiatric ward (RR = 1.74; 95% CI 1.13 to 2.68).

Follow-up at 7 months found a trend favouring greater abstinence (27.5%) in the drug dependency unit group compared with the general psychiatric ward group (13.3%) (RR = 2.07; 95% CI 0.77 to 5.55).

A number of significant limitations to this study raise questions as to whether differences in outcome were due to the setting or some other confounding factor and therefore preclude any specific recommendations arising from this study. Firstly, different medication was used for detoxification in the drug dependency unit (methadone) and general psychiatric ward (clonidine) groups; therefore there is some

uncertainty over whether the reported differences in outcome were due to the setting or the medication. In addition, all participants had previously been referred to a specialist service, thus allocation to a general psychiatric ward may have contributed towards resistance, a higher dropout rate and poorer outcomes.

8.2.5 Specialist community-based versus generic community-based

Only one study (Gibson *et al.*, 2003) from Australia compared community-based buprenorphine detoxification in a specialist clinic setting with a similar regimen in a primary care setting (5-day detoxification with assessment on day 8). Participants attended daily to receive a supervised dose of buprenorphine. The primary care group received their doses from the GP's surgery on weekdays and from the specialist clinic at weekends. The specialist clinic group received all their doses from this setting. At each visit, practitioners were encouraged to review side effects, dose adequacy, participants' goals and post-detoxification treatment options. They found that the settings had similar efficacy and cost effectiveness: with 71% completing detoxification in the primary care setting and 78% in the specialist clinic setting (RR = 1.09; 95% CI, 0.88 to 1.35). Additionally, 23% reported no opioid use during detoxification treatment in the primary care group compared with 22% in the specialist clinic group (RR = 0.95; 95% CI, 0.48 to 1.87).

There are no published UK studies comparing detoxification in primary and secondary care, although the above study would suggest there are no differences in outcome or cost effectiveness between primary and secondary care settings.

8.2.6 Predictors of outcome in inpatient settings

Information about the databases searched and inclusion/exclusion criteria can be found in Table 34.

Table 34: Databases searched and inclusion/exclusion criteria for predictors of outcome in inpatient detoxification

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005–January 2007
Study design	RCT Observational studies
Patient population	Opioid dependent
Interventions	Detoxification in the following settings: inpatient, residential
Outcomes	Abstinence, treatment completion

In the review of predictors of outcome for inpatient settings, five studies met the criteria set by the GDG (Araujo *et al.*, 1996; Backmund *et al.*, 2001; Franken & Hendriks, 1999; Hattenschwiler *et al.*, 2000; Perez de los Cobos *et al.*, 1997). All studies were published in peer-reviewed journals.

Several studies have looked at both service user and programme factors that may predict outcome in service users presenting for inpatient detoxification. Franken and Hendriks (1999) in a study of 175 service users found that greater severity of drug use was associated with lower completion rates for inpatient detoxification (OR = 9.0; 95% CI, 4.50 to 17.75). Similarly, in a study of 275 service users entering inpatient detoxification, Perez de los Cobos and colleagues (1997) found more frequent cocaine use was associated with discharge against medical advice from a detoxification programme (OR = 3.81; 95% CI, 1.30 to 11.04). Franken and Hendriks also found that severe physical health problems predicted poor completion outcomes (OR = 9.3; 95% CI, 4.72 to 18.63). Backmund and colleagues (2001) reviewed the records of 1,070 patients admitted for inpatient detoxification and found that outcomes were better in service users already on methadone maintenance treatment (50.4% completed) compared with those (35.9%) who primarily injected heroin (RR = 1.40, 95% CI, 1.11 to 1.77). Measures of social stability, such as lack of social integration ($r = -0.26$) (Hattenschwiler *et al.*, 2000) and being single ($\chi^2 = 4.32$, $p < .05$) (Perez de los Cobos *et al.*, 1997), were also associated with poor completion outcomes.

Process factors such as the perceived suitability ($F = 16.63$, $p < 0.001$) of a treatment programme (Franken & Hendriks, 1999) were found to predict positive completion outcomes. Backmund and colleagues (2001) found a positive dose–response relationship between the amount of psychosocial or psychotherapeutic support and completion of detoxification.

Regarding psychopathology as a possible predictor, Araujo and colleagues (1996) failed to show any relationship between anxiety (SMD = 0.16; 95% CI, −0.18 to 0.50) or depression (SMD = 0.07; 95% CI, −0.27 to 0.41) in completion of detoxification. Franken and Hendriks (1999) found that psychopathology, coping styles and sociodemographic variables failed to predict the outcome of detoxification.

The studies considered above are process studies only, with no formal clinical trials available. It would seem that using fewer combinations of drugs in lower quantities and being more socially stable at admission predicts a better outcome from inpatient detoxification. There seems to be an uncertain relationship between psychopathology and outcome. However, it should be noted that, although the studies suggest that service users with better prognostic factors do well, there is no research to address whether people with poorer prognostic factors would benefit greater from alternative treatment settings or additional input in those settings. Some participants may have had poor prognostic factors, compared with other participant groups, but still benefited more from inpatient treatment than they would have done in the community.

8.2.7 Literature review of health economics evidence

The systematic literature review identified two studies that assessed the cost effectiveness of detoxification treatment in different settings (Gossop & Strang, 2000 and Shanahan *et al.*, 2006). Full references, characteristics and results of all studies included in the economic review are presented in the form of evidence tables in Appendix 14.

Gossop and Strang (2000) performed a reanalysis of data from two randomised trials assessing opioid detoxification treatments in different settings. A crude economic analysis was done, using completion rates as the outcome measure against which costs were examined. In the first analysis, the cost of the inpatient detoxification was 24 times more than that of the outpatient treatment, but when adjusted for successful achievement for abstinence costs were almost identical.

In the second analysis, completion rates were 45% and 18% of the original cohort for the specialist inpatient unit and the general psychiatric ward respectively. Costs in the specialist unit were three times more than the general ward, but after accounting for completion rates the ratio was 1.9:1. Even though the analysis was based on crude estimates and may have not expanded to other settings, the authors concluded that provision of 10-day inpatient detoxification was as cost effective as the outpatient detoxification programme. In addition, they suggested that inpatient detoxification was easier and cheaper to run in a general psychiatric ward rather than in a specialist unit.

A cost-effectiveness analysis of heroin detoxification methods in Australia was performed by Shanahan and colleagues (2006). Five inpatient and outpatient detoxification methods were compared using data from four trials involving 365 people using heroin. The study assessed the achievement of an initial 7-day period of abstinence as well as entry into ongoing post-detoxification treatment. The base comparator for the analysis was conventional outpatient detoxification; other comparators included: conventional inpatient, rapid detoxification under sedation, rapid detoxification under anaesthesia and buprenorphine. Mean costs for all methods analysed were calculated. Buprenorphine outpatient detoxification was the least expensive method per episode ($491), the most expensive being rapid detoxification under anaesthesia ($2,689). In terms of abstinence, rapid detoxification under anaesthesia and rapid detoxification under sedation were equivalent (59%) with levels of abstinence significantly higher than conventional inpatient (24%), buprenorphine (12%) and conventional outpatient (4%). The incremental cost-effectiveness analysis found that buprenorphine-based outpatient detoxification was the most cost effective overall. Indeed, buprenorphine was the only treatment that at the same time was more effective and less costly than the base comparator, conventional outpatient. Rapid opioid detoxification under sedation was the most cost-effective inpatient method.

The choice of setting for opioid detoxification has major resource implications. Effectiveness data comparing inpatient versus community detoxification are poor and do not indicate significant differences between them in terms of abstinence. Inpatient treatment is substantially more expensive compared with community detoxification, due to hospitalisation costs and more intensive pharmacological regimes. As a consequence, and in light of the very poor evidence for increased cost effectiveness for inpatient

services and the lack of information on particular patient sub-groups, the current data would suggest that community detoxification should be provided as first-line treatment.

8.2.8 Clinical practice recommendations

The choice of setting for detoxification

8.2.8.1 Staff should routinely offer a community-based programme to all service users considering opioid detoxification. Exceptions to this may include service users who:

- have not benefited from previous formal community-based detoxification
- need medical and/or nursing care because of significant comorbid physical or mental health problems
- require complex polydrug detoxification, for example concurrent detoxification from alcohol or benzodiazepines
- are experiencing significant social problems that will limit the benefit of community-based detoxification.

8.2.8.2 Residential detoxification should normally only be considered for people who have significant comorbid physical or mental health problems, or who require concurrent detoxification from opioids and benzodiazepines or sequential detoxification from opioids and alcohol.

8.2.8.3 Residential detoxification may also be considered for people who have less severe levels of opioid dependence, for example those early in their drug-using career, or for people who would benefit significantly from a residential rehabilitation programme during and after detoxification.

8.2.8.4 Inpatient, rather than residential, detoxification should normally only be considered for people who need a high level of medical and/or nursing support because of significant and severe comorbid physical or mental health problems, or who need concurrent detoxification from alcohol or other drugs that requires a high level of medical and nursing expertise.

8.2.8.5 Following successful opioid detoxification, and irrespective of the setting in which it was delivered, all service users should be offered continued treatment, support and monitoring designed to maintain abstinence. This should normally be for a period of at least 6 months.

Delivering detoxification

8.2.8.6 Community detoxification should normally include:

- prior stabilisation of opioid use through pharmacological treatment
- effective coordination of care by specialist or competent primary practitioners
- the provision of psychosocial interventions, where appropriate, during the stabilisation and maintenance phases.

8.2.8.7 Inpatient and residential detoxification should be conducted with 24-hour medical and nursing support commensurate with the complexity of the service user's drug misuse and comorbid physical and mental health problems.

Both pharmacological and psychosocial interventions should be available to support treatment of the drug misuse as well as other significant comorbid physical or mental health problems.

8.2.9 Research recommendation – comparing inpatient or residential and community detoxification

8.2.9.1 Is inpatient or residential detoxification associated with greater probability of abstinence, better rates of completion of treatment, lower levels of relapse and increased cost effectiveness than community detoxification?

Why this is important

There have been some studies comparing inpatient or residential detoxification with community detoxification. However, these studies are often based on small sample sizes, have considerable methodological problems and have produced inconsistent results. Inpatient or residential detoxification requires significantly more resources than community detoxification, so it is important to assess whether treatment in such settings is more clinically and cost effective. If so, it is also important to understand if there are particular subgroups that are more likely to benefit from treatment in these settings.

8.3 UNASSISTED/SELF-DETOXIFICATION

Unassisted or self-detoxification, defined as 'the deliberate attempt to achieve abstinence from drugs which is sustained for longer than 24 hours in the absence of clinical assistance' (Gossop *et al.*, 1991; Noble *et al.*, 2002), has been a subject of concern for some time, not least because it is clear from epidemiological studies that a significant number of people stop misusing opioids without formal treatment. However, it is not clear if these people who attempt to self-detoxify are likely to experience more harm or to be less successful than those undergoing professional detoxification procedures. In addition, the study of unassisted detoxification may provide some understanding of what contributes to successful detoxification and thereby potentially improve the outcomes for assisted detoxifications.

8.3.1 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/exclusion criteria used can be found in Table 35.

8.3.2 Studies considered

The review team conducted a new systematic search for observational and non-comparative studies that assessed the efficacy of unassisted detoxification.

Table 35: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological interventions

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005–January 2007
Study design	Observational studies Non-comparative studies
Patient population	Opioid dependent
Interventions	Unassisted detoxification
Outcomes	Abstinence, treatment completion

Four interview-based studies (Gossop *et al.*, 1991; Ison *et al.*, 2006; Noble *et al.*, 2006; Scherbaum *et al.*, 2005) documented service users' experiences of previous attempts at unassisted detoxification.

In addition, five studies were excluded from the analysis. The most common reason for exclusion was that they were not directly related to detoxification.

8.3.3 Experiences of unassisted detoxification

While it is common practice for individuals wishing to terminate drug use to self-detoxify, there is little documentation of the methods by which they do this and their respective success rates (Gossop *et al.*, 1991). Several authors have retrospectively investigated dependent drug users' previous unassisted detoxification attempts (Gossop *et al.*, 1991; Ison *et al.*, 2006; Noble *et al.*, 2002; Scherbaum *et al.*, 2005). The main limitation of this approach is selection bias in that participants selected for the study represent those who are currently engaged with services and therefore have not benefited from unassisted detoxification. Thus it is difficult to discern the true numbers of those who have successfully self-detoxified from this sample.

Gossop and colleagues (1991) examined the frequency of and circumstances associated with unassisted detoxification attempts, the methods employed and subsequent rates of abstinence. Within a sample of 50 dependent opioid users, attempts to self-detoxify involved either abrupt cessation of drugs or detoxification with self-administered drugs including benzodiazepines and opioids. Of the 212 documented unassisted detoxification attempts, 24% resulted in abstinence lasting one week or more, 14% lasting 4 weeks or more and 3% lasting 1 year or more. There were no differences in outcomes for abrupt cessation versus detoxification with the aid of drugs; these were comparable with results for outpatient detoxification.

Employing a larger data-set, Noble and colleagues (2002) extended Gossop and colleagues' (1991) findings. A total of 114 participants completed structured

interviews regarding their personal experiences of unassisted detoxification. Of these, 58% had previously attempted unassisted detoxification with a mean of 3.6 attempts per individual. There were no significant demographic or gender differences between this group and those who had never attempted unassisted detoxification. Of the 66 who had attempted unassisted detoxification, 38% had never succeeded in achieving 24 hours of abstinence.

The majority (76%) of unassisted detoxification attempts were made at home, often with the aid of drugs such as diazepam (43%), methadone (22%), cannabis (22%), or alcohol (25%). The most common motives for initiating unassisted detoxification were frustration with the current drug-taking lifestyle and family pressure. Around 25% of participants felt that they did not need formal help with detoxification and often perceived waiting times for formal treatment to be too long.

When comparing length of time abstinent after the most recent detoxification attempt between less than 1 week (n = 35) and more than 1 week (n = 31), the groups did not differ in terms of age, age at first injection or number of attempts at unassisted detoxification. However, those who achieved more than 1 week of abstinence after the last unassisted detoxification attempt had initiated heroin use at a significantly younger age (mean 17.7 years) than those who achieved less than 1 week's abstinence (mean 21.1 years). Individuals with a longer drug use history may be better equipped to self-detoxify.

Scherbaum and colleagues (2005) investigated the unassisted detoxification experiences of 142 dependent opioid users. In total, 23% of participants reported use of illicitly acquired methadone to self-detoxify or to bridge the waiting period for formal treatment. Similar findings were reported by Ison and colleagues (2006). Among a sample of 98 opioid-dependent users, the most common reason for not accessing medically assisted detoxification was the length of the waiting list for formal treatment. Furthermore, relapse into drug use often occurred as a result of the severity of withdrawal symptoms. Thus, preventing relapse may be achieved by directing attention to ways in which to overcome persistent withdrawal symptoms.

Overall, the findings suggest that greater emphasis should be placed on making formal detoxification treatment more readily available for individuals wishing to detoxify, which could potentially reduce both demand for illicit methadone and unassisted detoxification attempts.

It must be noted that all of the detoxification attempts reported in the previous studies eventually failed, as participants were drawn from a population currently drug dependent or seeking treatment. Therefore it is difficult to assess if there are any positive outcomes associated with unassisted detoxification. Further research into the methods and circumstances of these detoxifications could be very informative.

8.3.4 Clinical practice recommendation

8.3.4.1 People who are opioid dependent and considering self-detoxification should be encouraged to seek detoxification in a structured treatment programme or, at a minimum, to maintain contact with a drug service.

8.4 PRISON-BASED DETOXIFICATION

As was noted in the introduction to this chapter, an increasingly active role is being taken by the prison services in the treatment of individuals with opioid misuse problems. For the majority of drug users, this may involve assessment, stabilisation, the provision of appropriate maintenance treatment and referral onto community-based services following release from prison. However, as the prison drug service develops its drug treatment capacity so there is an increasing opportunity to offer detoxification programmes to people who misuse opioids.

8.4.1 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/exclusion criteria used for this section of the guideline can be found in Table 36.

Table 36: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological interventions

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library, HMIC
Date searched	Database inception to November 2006; table of contents November 2005–January 2007
Study design	RCT Observational studies
Patient population	Opioid dependent
Interventions	Prison-based detoxification
Outcomes	Abstinence, treatment completion

8.4.2 Studies considered

The review team conducted a new systematic search for RCTs and observational studies that assessed the efficacy of prison-based detoxification. No studies met the eligibility criteria set by the GDG. One study was excluded because it primarily assessed pharmacological efficacy rather than the specific issues associated with prison-based detoxification.

8.4.3 Clinical management of prison-based detoxification

No studies were identified that specifically assessed prison-based detoxification. However, a recent consensus-based document by the Prison Service (DH, 2006)

provided guidance on the clinical management of drug misuse in prisons. It points out that detoxification within a prison setting requires particular consideration with regard to the risks involved when providing clinical management to prisoners upon reception. Within the prison setting there is limited ability to adequately assess and confirm previous drug use, due to the late arrival of prisoners being received from the courts on a daily basis. In addition, prisoners in withdrawal are unlikely to provide reliable self-reports of their drug use, and formal confirmation of their level of use is often impossible to verify. The risk of opioid toxicity at the outset of treatment is therefore ever present.

Detoxification resulting in abstinence from opioids can place prisoners at increased risk of post-release overdose (WHO, 2001). Again, this is a particular risk where prisoners have not made a positive decision to abstain from drugs, but have accepted the detoxification offered upon arrival in prison. These risks can be further exacerbated by the sudden unplanned release of a prisoner during treatment. There is also an acknowledged vulnerability of drug users to self-harm and die by suicide in prison, particularly during the first 28 days of custody. This risk could be increased by starting a detoxification programme at this stage.

8.4.4 Summary

The particular constraints of prison life require some modification of the programmes used in community and inpatient settings. However, apart from a greater degree of uncertainty surrounding the assessment of recent drug use, most centre on the limitations imposed by the uncertainty about many prisoners' duration of stay in a particular prison, especially those on remand. This suggests the need for considerable caution in the use of detoxification programmes, particularly for those who are recently admitted to prison or who are nearing release.

8.4.5 Clinical practice recommendation

8.4.5.1 People in prison should have the same treatment options for opioid detoxification as people in the community. Healthcare professionals should take into account additional considerations specific to the prison setting, including:

- practical difficulties in assessing dependence and the associated risk of opioid toxicity early in treatment
- length of sentence or remand period, and the possibility of unplanned release
- risks of self-harm, death or post-release overdose.

9. APPENDICES

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APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

Final version

28 September 2005

GUIDELINE TITLE

Drug misuse: opiate detoxification of drug misusers in the community, hospital and prison.[12]

Short title

Drug misuse – detoxification.

BACKGROUND

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Mental Health to develop a clinical guideline on opiate[13] detoxification of drug misusers[14] in the community, hospital and prison settings for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see Appendix [to the scope] below). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute has simultaneously commissioned the National Collaborating Centre for Mental Health to develop a clinical guideline on psychosocial interventions for people who misuse drugs in the community and in prison settings for use in the NHS in England and Wales.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published.

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[12]The guideline title changed during the development process to *Drug Misuse: Opioid Detoxification.*

[13]The term *opiates* has been replaced with the generic term *opioids* throughout the guideline, with the exception of the scope (where it originally appeared) and where the term relates specifically to the subset of opioids that are naturally occurring or semi-synthetic derivatives of the opium poppy, including heroin.

[14]The term *drug misusers* has been replaced with *people who misuse drugs* throughout the guideline, with the exception of the scope, where it originally appeared.

The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

CLINICAL NEED FOR THE GUIDELINE

The term opiate is used throughout this scope. Although this term normally implies substances containing natural opium, in this scope the term is used more broadly to include opioids (synthetic substances with similar properties).

It is estimated that there are between 250,000 and 500,000 problem drug users in the United Kingdom, of whom about 125,500 are in treatment in any year. There is a government target of ensuring 200,000 are in effective treatment in 2008. The majority of those requiring treatment are opiate dependent (and currently or previously using illicit heroin), although the use of other drugs such as stimulants (for example, cocaine) is known to be increasing.

Severe opiate dependence is a disorder of multi-factorial aetiology, with multiple and varied perpetuating factors. It has a central feature of psychological reinforcement of repeated drug-taking behaviour and it also has a marked withdrawal syndrome. Disturbances of the brain reward pathways may be important underlying pathological mechanisms. For this reason, it is usually considered that a range of interventions may be required in addition to pharmacological treatments.

There may be associated problems of family, social, criminal justice difficulties, health problems including blood borne viruses and other drug and alcohol problems. Families themselves may be affected by the drug misuse and are often a major resource in resolving problems and supporting the family member through treatment.

For people with severe drug dependency and others with long-standing dependency, the disorder has characteristics as a long-term chronic relapsing disorder with periods of remission and relapse, so while abstinence may be one of a range of long-term goals of treatment this is not always achieved. Even when abstinence is achieved, the benefits are not always maintained, and periods of relapse may still occur.

The evidence for detoxification programmes including the use of a range of pharmacological treatments (including methadone, buprenorphine and lofexidine) and the appropriate settings in which to best provide these interventions is not as strong as the evidence for maintenance and harm-reduction programmes.

The societal costs of drug misuse have been estimated at many billions of pounds, with opiate dependence and use of Class A drugs constituting the main cause of these costs.

Opiate substitution therapies (methadone and buprenorphine are most commonly used) allow the patient to replace street heroin with a longer-acting, less euphoriant

and safer drug while avoiding the withdrawal syndrome. Once stabilised, many patients remain on maintenance treatment, which brings improvements in illicit drug use, physical health, well-being, social stabilisation and reduced criminality and costs to society.

People who misuse drugs in prison sometimes receive assistance with withdrawal symptoms and some receive a treatment programme in prison. Access to regular high levels of illicit drugs in prisons is limited, so most people with drug dependency lose tolerance and are at risk of overdose if – as commonly happens – they begin using again on release.

Determining when to offer detoxification and where to provide it is often a difficult clinical decision. Clarity about the purpose of any treatment strategy is crucial because confusion between detoxification and maintenance programmes can lead to a lack of clear treatment aims and a poorer quality of care.

THE GUIDELINE

The guideline development process is described in detail in two publications which are available from the NICE website (see 'Further information'). *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (Second Edition)* (NICE, 2006b) describes how organisations can become involved in the development of a guideline. *The Guidelines Manual* (NICE, 2006a) provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see Appendix [to the scope] below). The areas that will be addressed by the guideline are described in the following sections.

POPULATION

Groups that will be covered

- adults and young people who are dependent on opiates and have been identified as suitable for a detoxification programme.

Groups that will not be covered

- adults and young people whose primary drug of misuse is a non-opiate
- adults and young people who misuse alcohol, where the primary diagnosis and focus of intervention is alcohol misuse
- adults and young people who misuse other prescription drugs – for example, benzodiazepines
- adults and young people who misuse solvents (for example, aerosols and glue) or other street drugs (for example, LSD [lysergic acid diethylamide])
- adults and young people prescribed opiates and related drugs for therapeutic purposes unrelated to substance misuse.

HEALTHCARE SETTING

The guideline will be of relevance to the NHS and related organisations, including:

- prison services
- inpatient and specialist residential and community-based treatment settings.

This is an NHS guideline. Although it will comment on the interface with other services such as those provided by social services, educational services and the voluntary sector, it will not provide specific recommendations directed solely to non-NHS services, except insofar as they are provided under contract to the NHS.

CLINICAL MANAGEMENT – AREAS THAT WILL BE COVERED

The guideline will cover the following areas of clinical practice and will do so in a way that is sensitive to the cultural, ethnic and religious backgrounds of people who misuse drugs/are drug dependent and their families and carers.

- The guideline will cover detoxification programmes for people who misuse opiates in community, residential, prison and inpatient settings including the type and duration of the programme.
- The guideline will identify the most appropriate programmes for specific populations of people who misuse opiates.
- The guideline will make recommendations on the use of methadone, buprenorphine, lofexidine and other related products in opiate detoxification programmes, and the dose and duration of use.
- The guideline will include the treatment and management of non-opiate drug and alcohol misuse in the context of an opiate detoxification programme.
- When referring to pharmacological treatments, the guideline will, wherever possible, recommend use within their licensed indications. However, where the evidence clearly supports it, recommendations for use outside the licensed indications may be made in exceptional circumstances.
- The guideline will include the appropriate use of psychosocial interventions to support detoxification programmes.
- The safety, side effects and other disbenefits of the interventions reviewed will be considered.
- The guideline will address the integration of the interventions reviewed with a broad approach to the care and treatment of people who misuse drugs/are drug dependent and their families and carers.
- The guideline will consider the separate needs of families and carers as well as addressing the potential positive contribution of family and carers in the treatment and support of people who misuse drugs/are drug dependent.
- The guideline will address the various needs for information of patients, families and carers, at different stages of their treatment and in different settings, including the role of self-help interventions and of support and self-help groups, and the importance of agreeing objectives with patients before they agree to treatment.

Appendix 1

CLINICAL MANAGEMENT – AREAS THAT WILL NOT BE COVERED

- The guideline will not consider diagnosis or primary prevention.
- The guideline will not consider pharmacological maintenance programmes.

STATUS

Scope

This is the final draft of the scope following consultation, which will be reviewed by the Guidelines Review Panel and the Institute's Guidance Executive.

The guideline will incorporate the following NICE guidance, which is published or in development:

Methadone and Buprenorphine for the Treatment of Opiate Drug Misuse. NICE Technology Appraisal. (Publication expected March 2007.)[15]

Naltrexone to Prevent Relapse in Drug Misuse. NICE Technology Appraisal. (Publication expected March 2007.)[16]

Drug Misuse: Psychosocial Management of Drug Misuse. NICE Clinical Guideline. (Publication expected July 2007.)[17]

Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care. NICE Clinical Guideline No. 1. (2002).

Anxiety: Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalised Anxiety Disorder) in Adults in Primary, Secondary and Community Care. NICE Clinical Guideline No. 22. (2004).

Depression: Management of Depression in Primary and Secondary Care. NICE Clinical Guideline No. 23. (2004).

Self-Harm: the Short-Term Physical and Psychological Management and Secondary Prevention of Self-Harm in Primary and Secondary Care. NICE Clinical Guideline No. 16. (2004).

GUIDELINE

The development of the guideline recommendations will begin in October 2005.

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[15]This technology appraisal has now been published with a different title: NICE (2006c) *Methadone and Buprenorphine for the Management of Opioid Dependence. Evaluation Report.* London: NICE.

[16]This technology appraisal has now been published with a different title: NICE (2006a) *Naltrexone for the Management of Opioid Dependence. Evaluation Report.* London: NICE.

[17]This guideline has now been published with a different title: NICE (2007) *Drug Misuse: Psychosocial Interventions. NICE Clinical Guideline no. 51.* London: NICE.

FURTHER INFORMATION

Information on the guideline development process is provided in:

- *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (Second Edition)*
- *The Guidelines Manual.*

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

Appendix – Referral from the Department of Health and Welsh Assembly Government

The Department of Health and Welsh Assembly Government asked the Institute to prepare a guideline for the NHS in England and Wales on opiate detoxification of drug misusers in the community, hospital and prison settings.

The guidance will:

- by using the evidence base examine the effectiveness and cost effectiveness of detoxification regimes for the management of opiate misusers
- identify those groups of drug misusers who are most likely to benefit from detoxification regimes, and
- identify the key components of the effectiveness of detoxification within a wider package of pharmacological interventions, and the overall care provided for the drug misuser.

APPENDIX 2: DECLARATIONS OF INTEREST BY GUIDELINE DEVELOPMENT GROUP MEMBERS

With a range of practical experience relevant to drug misuse in the GDG, members were appointed because of their understanding and expertise in healthcare for people who misuse drugs and support for their families and carers, including: scientific issues; health research; the delivery and receipt of healthcare, along with the work of the healthcare industry; and the role of professional organisations and organisations for people who misuse drugs and their families and carers.

To minimise and manage any potential conflicts of interest, and to avoid any public concern that commercial or other financial interests have affected the work of the GDG and influenced guidance, members of the GDG must declare as a matter of public record any interests held by themselves or their families that fall under specified categories (see below). These categories include any relationships they have with the healthcare industries, professional organisations and organisations for people who misuse drugs and their families and carers.

Individuals invited to join the GDG were asked to declare their interests before being appointed. To allow the management of any potential conflicts of interest that might arise during the development of the guideline, GDG members were also asked to declare their interests at each GDG meeting throughout the guideline development process. The interests of all the members of the GDG are listed below, including interests declared prior to appointment and during the guideline development process.

CATEGORIES OF INTEREST

- **Paid employment**
- **Personal interests related to drug misuse**: payment in cash or kind and/or funding from the drug misuse-related healthcare industry, including consultancies, grants, fee-paid work and shareholdings or other beneficial interests.
- **Personal interests not specifically related to drug misuse:** any other payment and/or funding from the healthcare industry, including consultancies, grants and shareholdings or other beneficial interests.
- **Non-personal interests**: funding from the healthcare industry received by the GDG member's organisation or department, but where the GDG member has not personally received payment, including fellowships and other support provided by the healthcare industry.
- **Personal non-monetary interests:** these include, but are not limited to, clear opinions or public statements you have made about drug misuse, holding office in a professional organisation or advocacy group with a direct interest in drug misuse, other reputational risks relevant to drug misuse.

- **Personal family interests:** payments in cash or kind that were received by a member of your family.
- **Other interests relating to drug misuse:** funding from governmental or non-governmental organisations, charities, and so on, and/or ownership in a company that provides therapy or treatments likely to be covered in the guideline.

Declarations of interest	
Dr Clare Gerada – Chair, Guideline Development Group	
Employment	General Practitioner, Lambeth Primary Care, Trust, London Practice; Primary Care Lead for Drug Misuse and Chair at the Royal College of General Practitioners
Personal interests related to drug misuse	Member of Suboxone Expert Group at Schering-Plough (attended two meetings, received payment of £1000); member of Specialist Opioid Advisory Group at Napp Pharmaceuticals (reimbursed expenses for attending only)
Personal interests not specifically related to drug misuse	Member of Hepatitis C Expert Group at Roche (attended two meetings, received payment of £800)
Non-personal interests	Royal College of General Practitioners received funding from Schering-Plough for educational material
Personal non-monetary interests	Spoken publicly about heroin treatment: against heroin treatment until methadone treatment is adequately resourced
Personal family interests	None
Other interests related to drug misuse	Consultancy fees from Royal College of General Practitioners for training GPs in substance misuse; Advisor to Royal College of General Practitioners on all matters relating to substance misuse; Given evidence to General Medical Council on GPs' level of performance. Attended number of meetings run by Schering-Plough looking at feasibility of Suboxone as a treatment in the UK Attended Roche-funded hepatitis C meeting

Continued

Appendix 2

Declarations of interest (*Continued*)	
Mrs Pauline Bissett	
Employment	Retired (previously Chief Executive, Broadway Lodge until December 2006)
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Neil Connelly	
Employment	Voluntary Support Worker, Littledale Hall Therapeutic Community, Lancaster
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Paul Davis	
Employment	Consultant Lead Clinical Psychologist and Head of Psychology for Substance Misuse Services, Camden and Islington Mental Health and Social Care Trust
Personal interests related to drug misuse	None

Declarations of interest (*Continued*)	
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	Employed 1 day per week by National Treatment Agency for Substance Misuse as Clinical Psychology Advisor (September 2006–2008)
Personal family interests	None
Other interests related to drug misuse	Current grant funded projects: A study of the feasibility of routine screening and 'Stepped Care' psychological interventions with hazardous and problem drinkers in three inner London General Hospitals (London Health Action Zone 2003–2005, £47,000)
Ms Vivienne Evans	
Employment	Chief Executive, Adfam; Non-executive director of Charnwood and North West Leicestershire Primary Care Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	£6000 sponsorship from Schering-Plough to cover expenses of hosting Adfam's 21st birthday celebration, October 2005
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Emily Finch	
Employment	Addiction Psychiatrist, South London and Maudsley NHS Foundation Trust; Clinical Team Lead, National Treatment Agency for Substance Misuse

Continued

Declarations of interest (*Continued*)	
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	Trustee of Phoenix House
Personal family interests	None
Other interests related to drug misuse	Trustee of Phoenix House; Seconded two days per week to the NTA (October 2004 – January 2007)
Professor Robert Forrest	
Employment	Consultant in Clinical Chemistry and Toxicology, Sheffield Teaching Hospitals NHS Foundation Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	President of Forensic Science Society; Assistant Deputy Coroner, South Yorkshire (West); Programme Chair, Jurisprudence Section, American Academy of Forensic Sciences; expert witness in many cases where the issues are relevant to drug misuse; member of the editorial board for Science and Justice; member of Secretary of State's Medical Advisory Committee on Alcohol, Driving and Drugs
Personal family interests	None
Other interests related to drug misuse	Consultancy work (remitted to employer) for Forensic Alliance Ltd, now part of the Laboratory of the Government Chemist (LGC)

Declarations of interest (*Continued*)	
Dr Eilish Gilvarry	
Employment	Clinical Director, Newcastle Drug and Alcohol Unit, Newcastle upon Tyne
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr David Harding-Price	
Employment	Team Coordinator, Community Mental Health Team, Skegness, Lincolnshire
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	Eli Lilly 2005 funded mental health educational event at RCN congress; Janssen-Cilag 2005 sponsored European mental health educational conference
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Paul Hawkins	
Employment	None
Personal interests related to drug misuse	None

Continued

Declarations of interest (*Continued*)	
Personal interests not specifically related to drug misuse	None
Non-personal interests	Member of executive board for Cumbria Alcohol and Drugs Advisory Service
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Anne Lingford-Hughes	
Employment	Reader in Biological Psychiatry and Addiction, Academic Unit of Psychiatry, University of Bristol; Addiction Psychiatrist, Avon and Wiltshire Mental Health Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	Member of core faculty and steering group for Bristol-Myers Squibb, 2004, £2000; Honorarium from Janssen-Cilag for presentation, 2005; Honorarium from Bristol-Myers Squibb for plenary lecture, £499.23, 2007; Consultancy fee from Sanofi-Aventis, £1000, 2006; Health hearing systems for Johnson and Johnson Pharmaceutical services, 2003, £1451.72; Unrestricted grants for research; Merck, £50,000, 2004; Wyeth, £70,000, 2000
Non-personal interests	Psychopharmacology Unit, University of Bristol: Fellowship – Lundbeck; Within last 5 years department received various unrestricted grants from GSK, Astra-Zeneca, MSD, Wyeth, Novartis, Bristol-Myers Squibb
Personal non-monetary interests	Hon General Secretary of British Association for Psychopharmacology (BAP) – responsible for educational activities including opioid detoxification and coordinated BAP Consensus Guidelines, 2004, covering management of opioid detoxification.

Declarations of interest (*Continued*)	
Personal family interests	None
Other interests related to drug misuse	None
Ms Jan Palmer	
Employment	Nurse Consultant, Clinical Substance Misuse Lead, Offender Health
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mrs Kay Roberts	
Employment	Pharmacist; Chairman, PharMAG
Personal interests related to drug misuse	Wells Healthcare (for Schering-Plough) consultancy fees for training events; advisory board for Scotland: Suboxone, £800 in 2002, £360 in 2003; member of advisory board for Frontier Medical
Personal interests not specifically related to drug misuse	None
Non-personal interests	PharMAG receives in sponsorship and printing costs: Britannia Pharmaceuticals £250 per annum Reckitt Benckiser Ltd £1500, 2006; Rosemont Pharmaceuticals Ltd £1350, 2003–2005 Frontier Medical Ltd £250 per annum Cardinal Healthcare (Martindale Pharmaceuticals) £2000, 2006

Continued

Declarations of interest (*Continued*)	
Personal non-monetary interests	Royal College of General Practitioners, Lead Pharmacist (England) on Management of Substance Misuse in Primary Care; Royal College of General Practitioners (Scotland) tutor for Certificate in Management of Substance Misuse in Primary Care; Advisor to the Royal Pharmaceuticals Society of Great Britain on substance misuse; consultancy work for National Treatment Agency for Substance Misuse; member of the advisory council on misuse of drugs; member of UK Harm Reduction Alliance; member of Glasgow Children's Hearings Panel; member of International Harm Reduction Association; member of Scottish Medico-legal Society
Personal family interests	None
Other interests related to drug misuse	None

NCCMH STAFF

Mr Stephen Pilling – Facilitator, Guideline Development Group	
Employment	Joint Director, NCCMH; Director, Centre for Outcomes Research and Effectiveness, University College London; Consultant Clinical Psychologist and Deputy Head of Psychology Services, Camden and Islington Mental Health and Social Care Trust
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	Lecture for UK Psychiatric Pharmacy Group, October 2006, £300 including expenses; Lecture at Andrew Simms Centre, Leeds, December 2006, £300 including expenses
Non-personal interests	Grants for production of clinical guidelines and evidence-related practice: British Psychological Society Clinical Effectiveness Programme with Professor P. Fonagy and

	Professor S. Michie supporting production of NICE guidelines and related policy implementation work (£5.4 million, 2001–2010) Health service research grants: NHS Service Development and Organisation Research and Development Programme developing evidence-based and acceptable stepped-care systems in mental healthcare, an operational research project with Professor D. Richards, Professor S. Gallivan, Dr S. Gilbody, Professor K. Lovell, Dr J. Cape, Dr P. Bower and Ms J. Leibowitz (£299,642, 2006–2009); NHS Service Development and Organisation Research and Development Programme – The 100 Ward Study: a National Survey of Psychiatric Inpatient Unit Morale with Dr S. Johnson, Professor P. Bebbington, Professor M. King, Professor S. Woods, Professor N. Wellman, Dr D. Osborn and Dr R. Arraya (£296,999, 2006–2009)
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Sarah Hopkins	
Employment	Project Manager, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Rebecca King	
Employment	Project Manager, NCCMH (2005–2006)

Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Mr Ryan Li	
Employment	Research Assistant, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Nicholas Meader	
Employment	Systematic Reviewer, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None

Ms Poonam Sood	
Employment	Research Assistant, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Ms Sarah Stockton	
Employment	Information Scientist, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None
Dr Clare Taylor	
Employment	Editor, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None

Personal family interests	None
Other interests related to drug misuse	None
Mr Loukas Xaplanteris	
Employment	Health Economist, NCCMH
Personal interests related to drug misuse	None
Personal interests not specifically related to drug misuse	None
Non-personal interests	None
Personal non-monetary interests	None
Personal family interests	None
Other interests related to drug misuse	None

APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

The Guideline Development Group and the National Collaborating Centre for Mental Health review team would like to thank the following people who acted as advisors on specialist topics:

Ed Day	University of Birmingham
Michael Gossop	Institute of Psychiatry
Kim Wolff	Institute of Psychiatry

APPENDIX 4: STAKEHOLDERS WHO RESPONDED TO EARLY REQUESTS FOR EVIDENCE

Britannia Pharmaceuticals
Derbyshire Mental Health Services NHS Trust
Oxford and Buckinghamshire Mental Health Partnership NHS Trust
Pfizer
Rethink
Rosemont Pharmaceuticals
Royal College of Nursing
Royal College of Psychiatrists
Sheffield Teaching Hospitals NHS Foundation Trust

APPENDIX 5: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

Stakeholders
Altrix Healthcare plc
Birmingham Drug Action Team
Bolton Salford & Trafford Mental Health
British Association for Counselling and Psychotherapy (BACP)
British Psychological Society, The
CASPE Research
Department of Health
DrugScope
National Treatment Agency for Substance Misuse
North Staffordshire Combined Healthcare NHS Trust
Nottinghamshire Acute Trust
PharMAG
Release
Royal College of Midwives
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Schering-Plough Ltd
Specialist Clinical Addiction Network
Substance Misuse Management in General Practice
Western Counselling

Experts
None

APPENDIX 6: RESEARCHERS CONTACTED TO REQUEST INFORMATION ABOUT UNPUBLISHED OR SOON-TO-BE PUBLISHED STUDIES

Robert Ali
Seyed Assadi
Jenny Bearn
James Bell
David Best
Eric Collins
Jon Currie
Shane Darke
Cor De Jong
Detox 5
Michael Farrell
Bernard Favrat
Gilberto Gerra
Mark Gold
Michael Gossop
Paul Griffiths
Nick Heather
Paul Krabbe
Fergus Law
Walter Ling
Nicholas Lintzeris
Catherine McGregor
Lisa Marsch
John Marsden
Kenzie Preston
Duncan Raistrick
Alison Ritter
Roy Robertson
John Saunders
Udo Schneider
Juergen Seifert
Dwayne Simpson
Nora Volkow
Jason White

APPENDIX 7:
CLINICAL QUESTIONS

TOPIC GROUP 1: PHARMACOLOGICAL AND PHYSICAL INTERVENTIONS

1) For people who are opioid dependent, what detoxification treatments are associated with abstinence, completion of treatment and improvements on secondary outcomes (entry rate for naltrexone maintenance, use of other drugs, severity of withdrawal)?
   - 1.1) For people who are opioid dependent, what durations of detoxification treatment are associated with abstinence, completion of treatment and improvements on secondary outcomes (same as above)?

TOPIC GROUP 2: PSYCHOSOCIAL ADJUNCTS/PREDICTORS OF BENEFIT

2) For people who are opioid dependent, are there particular groups that are more likely to benefit from detoxification?
3) For people who are opioid dependent, are psychosocial interventions in combination with detoxification compared with detoxification with standard care associated with increased levels of abstinence, completion of treatment and improvements on secondary outcomes?

TOPIC GROUP 3: TREATMENT SETTING

4) For people who are opioid dependent, is inpatient detoxification in comparison with community-based detoxification associated with increased levels of abstinence, completion of treatment and improvements of secondary outcomes?
   - 4.1) For people who are opioid dependent, are there particular groups that respond better/worse to particular treatment settings?
5) For people who are opioid dependent and who are in prison, what detoxification treatment settings are associated with safety, abstinence, completion of treatment and improvements on secondary outcomes?
   - 5.1) For people who are opioid dependent and who are in contact with the community criminal justice system, what detoxification treatment settings are associated with abstinence, completion of treatment and improvements on secondary outcomes?

TOPIC GROUP 4: TESTING

6) For people in whom opioid dependence is suspected, are oral fluid and urine testing reliable methods, for example in terms of sensitivity and specificity, for identifying, confirming, quantifying and monitoring drug use?

7) In the context of opioid detoxification, what is good clinical practice in the assessment of dependence and monitoring of withdrawal?

   7.1) In the context of opioid detoxification, are there reliable and valid rating scales for the assessment of dependence and monitoring of withdrawal?

APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

1. GENERAL SEARCH FILTERS

Drug misuse

a. CINAHL, HMIC, EMBASE, MEDLINE, PsycINFO – OVID interface

1 exp narcotic dependence/ or exp opioid-related disorders/
2 (addiction or analgesic agent abuse or drug abuse or drug abuse pattern or drug dependenc$ or drug misuse or intravenous drug abuse or psychoses, substance-induced or substance abuse, intravenous or substance abuse, perinatal or substance abuse or substance dependence or substance withdrawal syndrome or substance-related disorders).sh.
3 "substance use disorders"/
4 ((drug$1 or substance$) adj3 (abstain$ or abstinen$ or abus$ or addict$ or dependen$ or disorder$ or intoxicat$ or misus$ or over dos$ or overdos$ or use$2 or using or withdraw$)).tw.
5 or/1-4
6 diamorphine/ or exp heroin/ or morphine/
7 exp narcotic agent/ or exp narcotics/ or exp narcotic drugs/
8 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin$ or morphacetin or morphine).mp. or 1502-95-0, 561-27-3.rn.
9 (anpec or duromorph or epimorph or morfin$ or morphia or morphin$ or morphinium or morphium or opso$1 or skenan).mp. or 57-27-2.rn.
10 opiate$.mp. or 8008-60-4.rn.
11 (opioid$ or opium or narcotic$).tw.
12 (abstain$ or abstinen$ or abus$ or addict$ or (excessive adj use$) or dependen$ or (inject$ adj2 drug$) or intoxicat$ or misus$ or over dos$ or overdos$ or (use$ adj (disorder$ or illicit)) or withdraw$).mp.
13 (or/6-11) and 12
14 or/5,13

b. Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley Interscience interface

#1	MeSH descriptor Opioid-Related Disorders explode all trees
#2	MeSH descriptor Substance-Related Disorders, this term only
#3	MeSH descriptor Substance Abuse, Intravenous, this term only
#4	MeSH descriptor Substance Withdrawal Syndrome, this term only
#5	MeSH descriptor Psychoses, Substance-Induced, this term only
#6	(drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): ti or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): ab or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*): kw
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8	MeSH descriptor Heroin, this term only
#9	MeSH descriptor Morphine explode all trees
#10	MeSH descriptor Narcotics explode all trees
#11	(acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ti or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ab or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):kw
#12	(anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ti or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ab or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):kw
#13	(opiate*):ti or (opiate*):ab or (opiate*):kw
#14	(opioid* or opium or narcotic*):ti or (opioid* or opium or narcotic*):ab or (opioid* or opium or narcotic*):kw
#15	(abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ti or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ab or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):kw
#16	((#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND #15)
#17	(#7 OR #16)

2. SYSTEMATIC REVIEW SEARCH FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

1 exp meta analysis/ or exp systematic review/ or exp literature review/ or exp literature searching/ or exp cochrane library/ or exp review literature/
2 ((systematic or quantitative or methodologic$) adj5 (overview$ or review$)).mp.
3 (metaanaly$ or meta analy$).mp.
4 (research adj (review$ or integration)).mp.
5 reference list$.ab.
6 bibliograph$.ab.
7 published studies.ab.
8 relevant journals.ab.
9 selection criteria.ab.
10 (data adj (extraction or synthesis)).ab.
11 ((handsearch$3 or (hand or manual)) adj search$).tw.
12 ((mantel adj haenszel) or peto or dersimonian or der simonian).tw.
13 (fixed effect$ or random effect$).tw.
14 review$.pt,mp. and (bids or cochrane or index medicus or isi citation or medlars or psyclit or psychlit or scisearch or science citation or web adj1 science).mp.
15 (systematic$ or meta$).pt.
16 or/1-15

3. RCT SEARCH FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

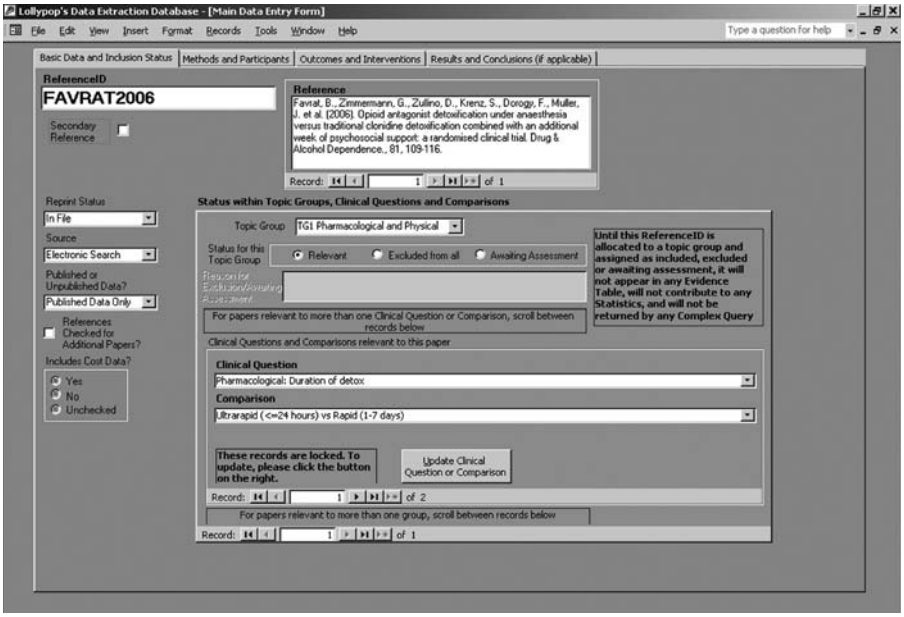
1 exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/
2 exp crossover procedure/ or exp cross over studies/ or exp crossover design/
3 exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/
4 exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/
5 exp randomized controlled trials/ or exp randomized controlled trial/
6 (clinical adj2 trial$).tw.
7 (crossover or cross over).tw.
8 (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
9 (placebo$ or random$).mp.
10 (clinical trial$ or clinical control trial or random$).pt.
11 animals/ not (animals/ and human$.mp.)

12	animal$/ not (animal$/ and human$/)
13	(animal not (animal and human)).po.
14	(or/1-10) not (or/11-13)

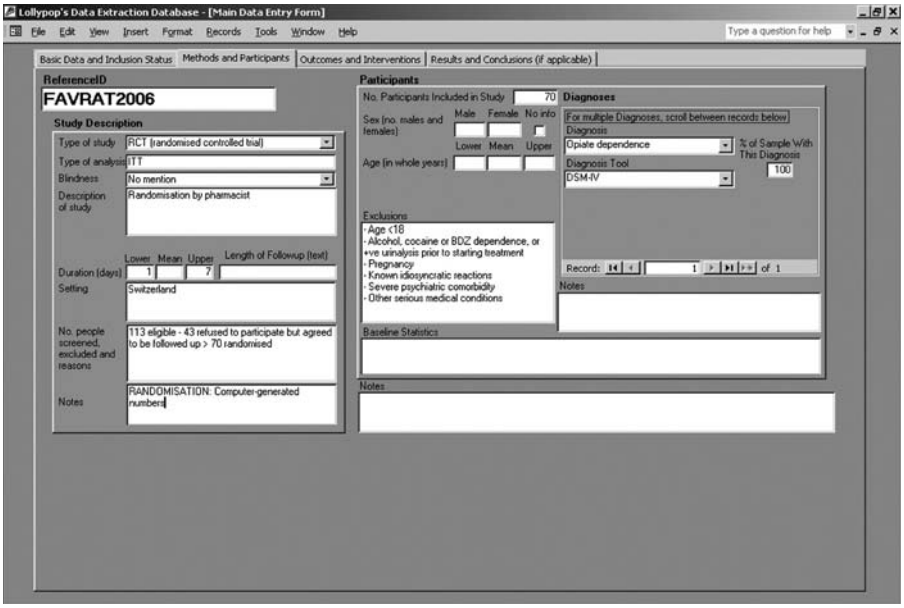
Details of additional searches undertaken to support the development of this guideline are available on request.

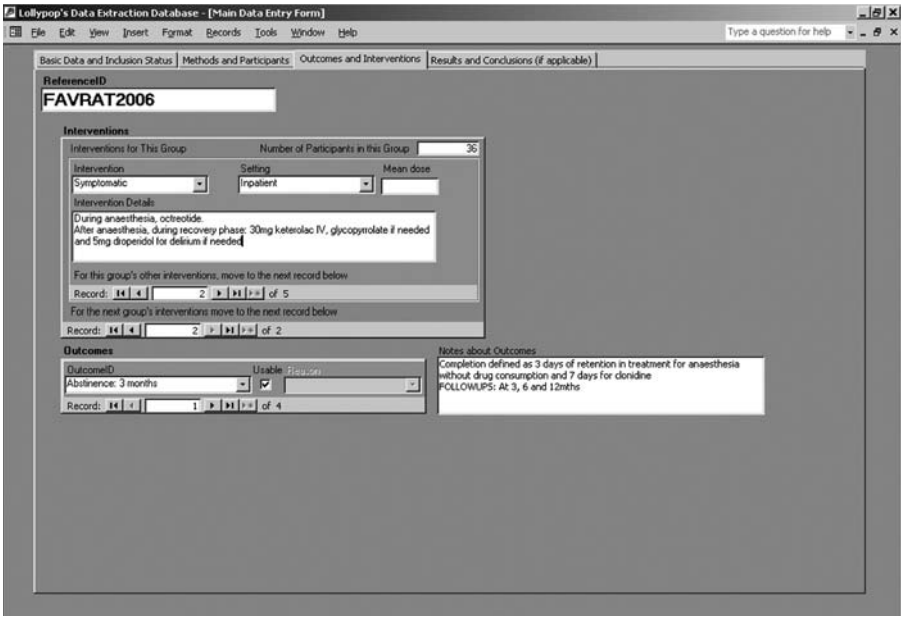
APPENDIX 9:
CLINICAL STUDY DATA EXTRACTION FORM

Information about each study was entered into an Access database using specially designed forms (see below for an example).



Appendix 9


Lollypop's Data Extraction Database - [Main Data Entry Form]
File Edit View Insert Format Records Tools Window Help
Type a question for help
Basic Data and Inclusion Status
Methods and Participants
Outcomes and Interventions
Results and Conclusions (if applicable)
ReferenceID
FAVRAT2006
Study Description
Type of study
RCT (randomised controlled trial)
Type of analysis
ITT
Blindness
No mention
Description of study
Randomisation by pharmacist
Duration (days)
Lower 1
Mean
Upper 7
Length of Followup (text)
Setting
Switzerland
No. people screened, excluded and reasons
113 eligible - 43 refused to participate but agreed to be followed up > 70 randomised
Notes
RANDOMISATION: Computer-generated numbers
Participants
No. Participants Included in Study 70
Sex (no. males and females)
Male
Female
No info
Age (in whole years)
Lower
Mean
Upper
Exclusions
- Age <18
- Alcohol, cocaine or BDZ dependence, or +ve urinalysis prior to starting treatment
- Pregnancy
- Known idiosyncratic reactions
- Severe psychiatric comorbidity
- Other serious medical conditions
Baseline Statistics
Notes
Diagnoses
For multiple Diagnoses, scroll between records below
Diagnosis
Opiate dependence
% of Sample With This Diagnosis
100
Diagnosis Tool
DSM-IV
Record: 1 of 1
Notes


Lollypop's Data Extraction Database - [Main Data Entry Form]
File Edit View Insert Format Records Tools Window Help
Type a question for help
Basic Data and Inclusion Status
Methods and Participants
Outcomes and Interventions
Results and Conclusions (if applicable)
ReferenceID
FAVRAT2006
Interventions
Interventions for This Group
Number of Participants in this Group 36
Intervention
Symptomatic
Setting
Inpatient
Mean dose
Intervention Details
During anaesthesia, octreotide.
After anaesthesia, during recovery phase: 30mg ketorolac IV, glycopyrrolate if needed and 5mg droperidol for delirium if needed
For this group's other interventions, move to the next record below
Record: 2 of 5
For the next group's interventions move to the next record below
Record: 2 of 2
Outcomes
OutcomeID
Abstinence: 3 months
Usable
Reason
Record: 1 of 4
Notes about Outcomes
Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine
FOLLOWUPS: At 3, 6 and 12mths

APPENDIX 10:
QUALITY CHECKLISTS FOR CLINICAL STUDIES AND REVIEWS

The methodological quality of each study was evaluated using dimensions adapted from SIGN (SIGN, 2002). SIGN originally adapted its quality criteria from checklists developed in Australia (Liddel *et al.*, 1996). Both groups reportedly undertook extensive development and validation procedures when creating their quality criteria.

Quality Checklist for a Systematic Review or Meta-Analysis			
Study ID:			
Guideline topic:		Key question no:	
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted systematic review:		In this study this criterion is: *(Circle one option for each question)*	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	A description of the methodology used is included.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Study quality is assessed and taken into account.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? *Code* ++, + *or* –		

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: SYSTEMATIC REVIEWS AND META-ANALYSES

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been

carried out carefully and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but insufficient detail to allow assessment to be made)
- not applicable.

1.1 THE STUDY ADDRESSES AN APPROPRIATE AND CLEARLY FOCUSED QUESTION

Unless a clear and well-defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question to be answered on the basis of the conclusions.

1.2 A DESCRIPTION OF THE METHODOLOGY USED IS INCLUDED

One of the key distinctions between a systematic review and a general review is the systematic methodology used. A systematic review should include a detailed description of the methods used to identify and evaluate individual studies. If this description is not present, it is not possible to make a thorough evaluation of the quality of the review, and it should be rejected as a source of level-1 evidence (though it may be useable as level-4 evidence, if no better evidence can be found).

1.3 THE LITERATURE SEARCH IS SUFFICIENTLY RIGOROUS TO IDENTIFY ALL THE RELEVANT STUDIES

A systematic review based on a limited literature search – for example, one limited to MEDLINE only – is likely to be heavily biased. A well-conducted review should at a minimum look at EMBASE and MEDLINE and, from the late 1990s onward, the Cochrane Library. Any indication that hand searching of key journals, or follow-up of reference lists of included studies, were carried out in addition to electronic database searches can normally be taken as evidence of a well-conducted review.

1.4 STUDY QUALITY IS ASSESSED AND TAKEN INTO ACCOUNT

A well-conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. If there is no indication of such an assessment, the review should be rejected as a source of level-1 evidence. If details of the assessment are poor, or the methods are considered to be inadequate, the quality of the review should be downgraded. In either case, it may be worthwhile obtaining and evaluating the individual studies as part of the review being conducted for this guideline.

1.5 THERE ARE ENOUGH SIMILARITIES BETWEEN THE STUDIES SELECTED TO MAKE COMBINING THEM REASONABLE

Studies covered by a systematic review should be selected using clear inclusion criteria (see question 1.4 above). These criteria should include, either implicitly or explicitly, the question of whether the selected studies can legitimately be compared. It should be clearly ascertained, for example, that the populations covered by the studies are comparable, that the methods used in the investigations are the same, that the outcome measures are comparable and the variability in effect sizes between studies is not greater than would be expected by chance alone.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

Appendix 10

Quality Checklist for an RCT			
Study ID:			
Guideline topic:		**Key question no:**	
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted RCT study:		**In this study this criterion is: (Circle one option for each question)**	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to treatment groups is randomised.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? *Code ++, + or –*		

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: RCTs

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but insufficient detail to allow assessment to be made)
- not applicable.

1.1 THE STUDY ADDRESSES AN APPROPRIATE AND CLEARLY FOCUSED QUESTION

Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question to be answered on the basis of its conclusions.

1.2 THE ASSIGNMENT OF SUBJECTS TO TREATMENT GROUPS IS RANDOMISED

Random allocation of patients to receive one or other of the treatments under investigation, or to receive either treatment or placebo, is fundamental to this type of study. If there is no indication of randomisation, the study should be rejected. If the description of randomisation is poor, or the process used is not truly random (for example, allocation by date or alternating between one group and another) or can otherwise be seen as flawed, the study should be given a lower quality rating.

1.3 AN ADEQUATE CONCEALMENT METHOD IS USED

Research has shown that where allocation concealment is inadequate, investigators can overestimate the effect of interventions by up to 40%. Centralised allocation, computerised allocation systems or the use of coded identical containers would all be regarded as adequate methods of concealment and may be taken as indicators of

a well-conducted study. If the method of concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating, and can be rejected if the concealment method is seen as inadequate.

1.4 SUBJECTS AND INVESTIGATORS ARE KEPT 'BLIND' ABOUT TREATMENT ALLOCATION

Blinding can be carried out up to three levels. In single-blind studies, patients are unaware of which treatment they are receiving; in double-blind studies, the doctor and the patient are unaware of which treatment the patient is receiving; in triple-blind studies, patients, healthcare providers and those conducting the analysis are unaware of which patients received which treatment. The higher the level of blinding, the lower the risk of bias in the study.

1.5 THE TREATMENT AND CONTROL GROUPS ARE SIMILAR AT THE START OF THE TRIAL

Patients selected for inclusion in a trial should be as similar as possible, in order to eliminate any possible bias. The study should report any significant differences in the composition of the study groups in relation to gender mix, age, stage of disease (if appropriate), social background, ethnic origin or comorbid conditions. These factors may be covered by inclusion and exclusion criteria, rather than being reported directly. Failure to address this question, or the use of inappropriate groups, should lead to the study being downgraded.

1.6 THE ONLY DIFFERENCE BETWEEN GROUPS IS THE TREATMENT UNDER INVESTIGATION

If some patients received additional treatment, even if of a minor nature or consisting of advice and counselling rather than a physical intervention, this treatment is a potential confounding factor that may invalidate the results. If groups were not treated equally, the study should be rejected unless no other evidence is available. If the study is used as evidence, it should be treated with caution and given a low quality rating.

1.7 ALL RELEVANT OUTCOMES ARE MEASURED IN A STANDARD, VALID AND RELIABLE WAY

If some significant clinical outcomes have been ignored, or not adequately taken into account, the study should be downgraded. It should also be downgraded if the measures used are regarded as being doubtful in any way or applied inconsistently.

1.8 WHAT PERCENTAGE OF THE INDIVIDUALS OR CLUSTERS RECRUITED INTO EACH TREATMENT ARM OF THE STUDY DROPPED OUT BEFORE THE STUDY WAS COMPLETED?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop-out rate is regarded as acceptable, but this may vary. Some regard should be paid to why patients dropped out, as well as how many. It should be noted that the drop-out rate may be expected to be higher in studies conducted over a long period of time. A higher drop-out rate will normally lead to downgrading, rather than rejection of a study.

1.9 ALL THE SUBJECTS ARE ANALYSED IN THE GROUPS TO WHICH THEY WERE RANDOMLY ALLOCATED (OFTEN REFERRED TO AS INTENTION-TO-TREAT ANALYSIS)

In practice, it is rarely the case that all patients allocated to the intervention group receive the intervention throughout the trial, or that all those in the comparison group do not. Patients may refuse treatment, or contra-indications arise that lead them to be switched to the other group. If the comparability of groups through randomisation is to be maintained, however, patient outcomes must be analysed according to the group to which they were originally allocated, irrespective of the treatment they actually received. (This is known as intention-to-treat analysis.) If it is clear that analysis was not on an intention-to-treat basis, the study may be rejected. If there is little other evidence available, the study may be included but should be evaluated as if it were a non-randomised cohort study.

1.10 WHERE THE STUDY IS CARRIED OUT AT MORE THAN ONE SITE, RESULTS ARE COMPARABLE FOR ALL SITES

In multi-site studies, confidence in the results should be increased if it can be shown that similar results were obtained at the different participating centres.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
−	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

Appendix 10

Quality Checklist for a Cohort Study*			
Study ID:		Relevant questions:	
Guideline topic:			
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted cohort study:		**In this study the criterion is:** (***Circle one option for each question***)	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SELECTION OF SUBJECTS			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?		
1.6	Comparison is made between full participants and those lost to follow-up, by exposure status.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
ASSESSMENT			
1.7	The outcomes are clearly defined.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	The assessment of outcome is made blind to exposure status.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	The measure of assessment of exposure is reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.12	Exposure level or prognostic factor is assessed more than once.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?		
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code ++, + or –*		

*A cohort study can be defined as a retrospective or prospective follow-up study. Groups of individuals are defined on the basis of the presence or absence of exposure to a suspected risk factor or intervention. This checklist is not appropriate for assessing uncontrolled studies (for example, a case series where there is no comparison [control] group of patients).

NOTES ON THE USE OF THE METHODOLOGY CHECKLIST: COHORT STUDIES

The studies covered by this checklist are designed to answer questions of the type 'What are the effects of this exposure?' It relates to studies that compare a group of people with a particular exposure with another group who either have not had the exposure or have a different level of exposure. Cohort studies may be prospective (where the exposure is defined and subjects selected before outcomes occur) or retrospective (where exposure is assessed after the outcome is known, usually by the examination of medical records). Retrospective studies are generally regarded as a weaker design, and should not receive a 2++ rating.

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully, and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that has been shown to make a significant difference to the conclusions of a study.

Because of the potential complexity and subtleties of the design of this type of study, there are comparatively few criteria that automatically rule out use of a study as evidence. It is more a matter of increasing confidence in the likelihood of a causal relationship existing between exposure and outcome by identifying how many aspects of good study design are present and how well they have been tackled. A study that fails to address or report on more than one or two of the questions considered below should almost certainly be rejected.

For each question in this section, one of the following should be used to indicate how well it has been addressed in the review:

- well covered
- adequately addressed
- poorly addressed
- not addressed (that is, not mentioned or indicates that this aspect of study design was ignored)
- not reported (that is, mentioned but insufficient detail to allow assessment to be made)
- not applicable.

1.1 THE STUDY ADDRESSES AN APPROPRIATE AND CLEARLY FOCUSED QUESTION

Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question to be answered on the basis of its conclusions.

1.2 THE TWO GROUPS BEING STUDIED ARE SELECTED FROM SOURCE POPULATIONS THAT ARE COMPARABLE IN ALL RESPECTS OTHER THAN THE FACTOR UNDER INVESTIGATION

Study participants may be selected from the target population (all individuals to which the results of the study could be applied), the source population (a defined subset of the target population from which participants are selected) or from a pool of eligible subjects (a clearly defined and counted group selected from the source population). It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status or the presence of specific prognostic factors or prognostic markers relevant to the study in question. If the study does not include clear definitions of the source populations and eligibility criteria for participants, it should be rejected.

1.3 THE STUDY INDICATES HOW MANY OF THE PEOPLE ASKED TO TAKE PART DID SO IN EACH OF THE GROUPS BEING STUDIED

This question relates to what is known as the participation rate, defined as the number of study participants divided by the number of eligible subjects. This should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of selection bias may be present, and the study results should be treated with considerable caution.

1.4 THE LIKELIHOOD THAT SOME ELIGIBLE SUBJECTS MIGHT HAVE THE OUTCOME AT THE TIME OF ENROLMENT IS ASSESSED AND TAKEN INTO ACCOUNT IN THE ANALYSIS

If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial, the final result will be biased. A well-conducted study will attempt to estimate the likelihood of this occurring and take it into account in the analysis through the use of sensitivity studies or other methods.

1.5 WHAT PERCENTAGE OF INDIVIDUALS OR CLUSTERS RECRUITED INTO EACH ARM OF THE STUDY DROPPED OUT BEFORE THE STUDY WAS COMPLETED?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop-out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop-out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop-out rate is a matter of judgement based on the reasons why people dropped out and whether drop-out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well-conducted study.

1.6 COMPARISON IS MADE BETWEEN FULL PARTICIPANTS AND THOSE LOST TO FOLLOW-UP BY EXPOSURE STATUS

For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well-conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. Any indication that differences exist should lead to the study results being treated with caution.

1.7 THE OUTCOMES ARE CLEARLY DEFINED

Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart disease in middle-aged men, for example, participants might be followed up until death, reaching a predefined age or until completion of the study. If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.

1.8 THE ASSESSMENT OF OUTCOME IS MADE BLIND TO EXPOSURE STATUS

If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done or not done adequately.

1.9 WHERE BLINDING WAS NOT POSSIBLE, THERE IS SOME RECOGNITION THAT KNOWLEDGE OF EXPOSURE STATUS COULD HAVE INFLUENCED THE ASSESSMENT OF OUTCOME

Blinding is not possible in many cohort studies. In order to assess the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups – for example, frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

1.10 THE MEASURE OF ASSESSMENT OF EXPOSURE IS RELIABLE

A well-conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.

1.11 EVIDENCE FROM OTHER SOURCES IS USED TO DEMONSTRATE THAT THE METHOD OF OUTCOME ASSESSMENT IS VALID AND RELIABLE

The inclusion of evidence from other sources or previous studies that demonstrate the validity and reliability of the assessment methods used should further increase the confidence in the quality of the study.

1.12 EXPOSURE LEVEL OR PROGNOSTIC FACTOR IS ASSESSED MORE THAN ONCE

Confidence in data quality should be increased if exposure level or the presence of prognostic factors is measured more than once. Independent assessment by more than one investigator is preferable.

1.13 THE MAIN POTENTIAL CONFOUNDERS ARE IDENTIFIED AND TAKEN INTO ACCOUNT IN THE DESIGN AND ANALYSIS

Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. A study that does not address the possibility of confounding should be rejected.

1.14 HAVE CONFIDENCE INTERVALS BEEN PROVIDED?

Confidence limits are the preferred method for indicating the precision of statistical results and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with caution.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on the responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

APPENDIX 11: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMICS EVIDENCE

1. GENERAL SEARCH FILTERS

Drug misuse

a. CINAHL, HMIC, EMBASE, MEDLINE, PsycINFO – OVID interface

1 exp narcotic dependence/ or exp opioid-related disorders/
2 (addiction or analgesic agent abuse or drug abuse or drug abuse pattern or drug dependenc$ or drug misuse or intravenous drug abuse or psychoses, substance-induced or substance abuse, intravenous or substance abuse, perinatal or substance abuse or substance dependence or substance withdrawal syndrome or substance-related disorders).sh.
3 "substance use disorders"/
4 ((drug$1 or substance$) adj3 (abstain$ or abstinen$ or abus$ or addict$ or dependen$ or disorder$ or intoxicat$ or misus$ or over dos$ or overdos$ or use$2 or using or withdraw$)).tw.
5 or/1-4
6 diamorphine/ or exp heroin/ or morphine/
7 exp narcotic agent/ or exp narcotics/ or exp narcotic drugs/
8 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin$ or morphacetin or morphine).mp. or 1502-95-0, 561-27-3.rn.
9 (anpec or duromorph or epimorph or morfin$ or morphia or morphin$ or morphinium or morphium or opso$1 or skenan).mp. or 57-27-2.rn.
10 opiate$.mp. or 8008-60-4.rn.
11 (opioid$ or opium or narcotic$).tw.
12 (abstain$ or abstinen$ or abus$ or addict$ or (excessive adj use$) or dependen$ or (inject$ adj2 drug$) or intoxicat$ or misus$ or over dos$ or overdos$ or (use$ adj (disorder$ or illicit)) or withdraw$).mp.
13 (or/6-11) and 12
14 or/5,13

b. NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (HTA) – Wiley Interscience interface

1 MeSH descriptor Opioid-Related Disorders explode all trees
2 MeSH descriptor Substance-Related Disorders, this term only
3 MeSH descriptor Substance Abuse, Intravenous, this term only
4 MeSH descriptor Substance Withdrawal Syndrome, this term only
5 MeSH descriptor Psychoses, Substance-Induced, this term only

6 (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):ti or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):ab or (drug* or substance*) near (abstain* or abstinen* or abus* or addict* or dependen* or disorder* or intoxicat* or misuse* or over dos* or overdos* or use or user* or using or withdraw*):kw

7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

8 MeSH descriptor Heroin, this term only

9 MeSH descriptor Morphine explode all trees

10 MeSH descriptor Narcotics explode all trees

11 (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ti or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):ab or (acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin* or morphacetin or morphin*):kw

12 (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ti or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):ab or (anpec or duromorph or epimorph or morfin* or morphia or morphin* or morphinium or morphium or opso* or skenan):kw

13 (opiate*):ti or (opiate*):ab or (opiate*):kw

14 (opioid* or opium or narcotic*):ti or (opioid* or opium or narcotic*):ab or (opioid* or opium or narcotic*):kw

15 (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ti or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):ab or (abstain* or abstinen* or abus* or addict* or (drug near use*) or (excessive* near use*) or dependen* or (inject* near drug*) or intoxicat* or misus* or over dos* or overdos* or (use* near (disorder* or illicit)) or withdraw*):kw

16 ((#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND #15)

17 (#7 OR #16)

c. Health Economic Evaluations Database (OHE HEED) – Wiley interface

1 AX = (stimulant* or drug* or substance) and (abstain* or abstinen* or abus* or addict* or dependen* or detox* or disorder* or intoxicat* or misuse* or overdos* or use* or using* or withdraw*)

2 AX = acetomorphine or diacephine or diacetylmorphine or diamorphine or diaphorin or heroin or morphacetin or morphine
3 AX = anpec or duromorph or epimorph or morfin* or morphia or morphin or morphinium or morphium or opso* or skenan
4 AX = opioid* or opium or narcotic* or opiate*
5 AX = abstain* or abstinen* or abus* or addict* or dependen* or intoxicat* or misus* or overdos* or withdraw* or 'disorder within 1 use' or 'disorder within 1 user' or 'disorder within 1 using' or 'disorders within 1 use' or 'disorders within 1 user' or 'disorders within 1 using' or 'drug within 2 use' or 'drug within 2 user' or 'excessive within 2 use' or 'excessive within 2 user' or 'excessively within 2 use' or 'excessively within 2 user' or 'illicit within 1 use' or 'illicit within 1 user' or 'illicit within 1 using' or 'illicitly within 1 use' 'illicitly within 1 user' or 'illicitly within 1 using' or 'inject drug' or 'inject drugs' or 'injecting drug' or 'injecting drugs'
6 CS = 2 OR 3 OR 4
7 CS = 5 AND 6
8 CS = 1 OR 7

2. HEALTH ECONOMIC AND QUALITY OF LIFE FILTERS

a. MEDLINE, EMBASE, PsycINFO, CINAHL – OVID interface

1 exp "costs and cost analysis"/ or "health care costs"/
2 exp health resource allocation/ or exp health resource utilization/
3 exp economics/ or exp economic aspect/ or exp health economics/
4 exp value of life/
5 (burden adj5 (disease or illness)).tw.
6 (cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or expenditure$ or economic$).tw.
7 (fiscal or funding or financial or finance or budget).tw.
8 (resource adj5 (allocation$ or utility$)).tw.
9 or/1-8
10 (value adj5 money).tw.
11 exp quality of life/
12 (qualit$3 adj5 (life or survival)).tw.
13 (wellbeing or health status or QOL).tw.
14 or/9-13

APPENDIX 12:
QUALITY CHECKLISTS FOR ECONOMIC STUDIES

1.1 FULL ECONOMIC EVALUATIONS

Author: **Date:**
Title:

	Study design	Yes	No	NA
1	The research question is stated	❑	❑	
2	The viewpoint(s) of the analysis are clearly stated	❑	❑	
3	The alternatives being compared are relevant	❑	❑	
4	The rationale for choosing the alternative programmes or interventions compared is stated	❑	❑	
5	The alternatives being compared are clearly described	❑	❑	
6	The form of economic evaluation used is justified in relation to the question addressed	❑	❑	
	Data collection			
1	The source of effectiveness data used is stated	❑	❑	
2	Details of the design and results of the effectiveness study are given	❑	❑	❑
3	The primary outcome measure(s) for the economic evaluation are clearly stated	❑	❑	
4	Methods to value health states and other benefits are stated	❑	❑	
5	Details of the subjects from whom valuations were obtained are given	❑	❑	
6	Indirect costs (if included) are reported separately	❑	❑	❑
7	Quantities of resources are reported separately from their unit costs	❑	❑	

8	Methods for the estimation of quantities and unit costs are described	❑	❑	
9	Currency and price data are recorded	❑	❑	
10	Details of currency of price adjustments for inflation or currency conversion are given	❑	❑	❑
11	Details of any models used are given	❑	❑	❑
12	The choice of model used and the key parameters on which it is based are justified	❑	❑	❑
	Analysis and interpretation of results			
1	Time horizon of costs and benefits is stated	❑	❑	
2	The discount rate(s) is stated	❑	❑	❑
3	The choice of rate(s) is justified	❑	❑	❑
4	An explanation is given if costs or benefits are not discounted	❑	❑	❑
5	Details of statistical tests and confidence intervals are given for stochastic data	❑	❑	❑
6	The approach to sensitivity analysis is given	❑	❑	
7	The choice of variables for sensitivity analysis is given	❑	❑	
8	The ranges over which the variables are varied are stated	❑	❑	
9	Relevant alternatives are compared	❑	❑	
10	Incremental analysis is reported	❑	❑	❑
11	Major outcomes are presented in a disaggregated as well as aggregated form	❑	❑	
12	The answer to the study question is given	❑	❑	
13	Conclusions follow from the data reported	❑	❑	
14	Conclusions are accompanied by the appropriate caveats	❑	❑	

1.2 PARTIAL ECONOMIC EVALUATIONS

Author: **Date:**
Title:

	Study design	Yes	No	NA
1	The research question is stated	❑	❑	
2	The viewpoint(s) of the analysis is clearly stated and justified	❑	❑	
	Data collection			
1	Details of the subjects from whom valuations were obtained are given	❑	❑	
2	Indirect costs (if included) are reported separately	❑	❑	❑
3	Quantities of resources are reported separately from their unit costs	❑	❑	
4	Methods for the estimation of quantities and unit costs are described	❑	❑	
5	Currency and price data are recorded	❑	❑	
6	Details of currency of price adjustments for inflation or currency conversion are given	❑	❑	❑
7	Details of any model used are given	❑	❑	❑
8	The choice of model used and the key parameters on which it is based are justified	❑	❑	❑
	Analysis and interpretation of results			
1	Time horizon of costs is stated	❑	❑	
2	The discount rate(s) is stated	❑	❑	❑

3	Details of statistical tests and confidence intervals are given for stochastic data	❑	❑	❑
4	The choice of variables for sensitivity analysis is given	❑	❑	
5	The ranges over which the variables are varied are stated	❑	❑	
6	Appropriate sensitivity analysis is performed	❑	❑	
7	The answer to the study question is given	❑	❑	
8	Conclusions follow from the data reported	❑	❑	
9	Conclusions are accompanied by the appropriate caveats	❑	❑	

APPENDIX 13:
DATA EXTRACTION FORM FOR ECONOMIC STUDIES

Reviewer: **Date of Review:**

Authors:

Publication Date:

Title:

Country:

Language:

Economic study design:

- ❑ CEA
- ❑ CBA
- ❑ CUA
- ❑ CMA
- ❑ CCA
- ❑ CA

Modelling:

- ❑ No
- ❑ Yes

Source of data for effect size measure(s):

- ❑ Meta-analysis
- ❑ RCT
- ❑ Quasi experimental study
- ❑ Cohort study
- ❑ Mirror image (before-after) study
- ❑ Expert opinion

Comments _____

Primary outcome measure(s) (please list):

_____

Interventions compared (please describe):

Treatment: _____

Comparator: _____

Setting (please describe):

_____

Patient population characteristics (please describe):

_____

_____

_____

Perspective of analysis:

❑ Societal
❑ Patient and family
❑ Healthcare system
❑ Healthcare provider
❑ Third party payer
❑ Other: _____

Time frame of analysis: _____

Cost data:

❑ Primary ❑ Secondary

If secondary please specify: _____

Costs included:

Direct medical	Direct non-medical	Lost productivity
❑ direct treatment	❑ social care	❑ income forgone due to illness
❑ inpatient	❑ social benefits	❑ income forgone due to death
❑ outpatient	❑ travel costs	❑ income forgone by caregiver
❑ day care	❑ caregiver out-of-pocket	
❑ community healthcare	❑ criminal justice	
❑ medication	❑ training of staff	

Or

❑ staff
❑ medication
❑ consumables
❑ overhead
❑ capital equipment
❑ real estate

Others: _____

Currency: _____ **Year of costing:** _____

Was discounting used?
❑ Yes, for benefits and costs ❑ Yes, but only for costs ❑ No

Discount rate used for costs: _____

Discount rate used for benefits:_____

Result(s):

_____

_____

_____

_____

Comments, limitations of the study:

_____

_____

_____

Quality checklist score (Yes/NA/All): ……/……/……

APPENDIX 14:
EVIDENCE TABLES FOR ECONOMIC STUDIES

Study, year and country	Intervention details	Study population setting study design – data source	Study type	Costs: description and values outcomes: description and values	Results: cost-effectiveness	Comments internal validity (Yes/No/NA) industry support
SHANA-HAN *et al.*, 2006	Intervention: Various detoxification methods (buprenor-phine outpatient, conventional inpatient, rapid detoxification) Comparator: conventional outpatient detoxification	Heroin users 18 years and over, seeking treatment Data source: four trials of heroin detoxification N = 365 Perspective: healthcare provider Australian quasi-experimental cohort study	Cost-effectiveness analysis	Costs (AUD$, 1999 prices): $491-buprenorphine outpatient, $605-conventional outpatient, $1404-conventional inpatient, $1990-rapid detoxification Outcomes: 7-day period of abstinence: RODA-58%, RODS-60%, conventional inpatient-24%, buprenorphine outpatient-12%, conventional outpatient-4%. Entry into post-detoxification treatment: RODA-42%, RODS-68%, conventional inpatient-12%, buprenorphine outpatient-65%, conventional outpatient-27%	Buprenorphine outpatient detoxification more cost effective overall. Rapid detoxification under sedation most cost effective inpatient treatment.	Sensitivity analysis: one-way Results were robust Discounting: not needed since time horizon for all analyses is less than 12 months. Internal validity:26/3/6
HARTZ *et al.*, 1999	Intervention: 180-day methadone detoxification enhanced with	Opioid dependent patients (N = 102) Participants were stabilised to a 80 mg methadone dose for	Cost effectiveness & cost-benefit analysis	Costs: cash credits can start from 35 cents and accumulate to a maximum of $755 at the end of treatment Cost of treatment was calculated for each participant individually	An incremental cost of $17.27 produced an additional 1% increase of abstinent	Failure to collect healthcare cost data for the full sample Small sample, extreme variance didn't provide

Continued

Study, year and country	Intervention details	Study population setting Study design – data source	Study type	Costs: description and values Outcomes: description and values	Results: cost effectiveness	Comments Internal validity (Yes/No/NA) Industry support
	contingency management Comparator: 180-day methadone detoxification	the first 4 months, followed by a 2-month taper		Total healthcare costs based on Medicare DRGs. Contingency management average cost: $3,278 (SD = 1003.29), STD average cost: $3,041 (SD = $1072.86)-not statistically significant difference Outcomes: continuous abstinence from drugs and alcohol during 4-month treatment	participants. For every additional $ spent there was a healthcare saving of $4.87. These are statistically insignificant differences.	enough power to achieve statistical significance. Discounting: not needed since time horizon was 4 months Internal validity: 20/5/10

GOSSOP, 2000	Detoxification of people who misuse opioids	People who misuse opioids Settings: 1. inpatient drug-dependence unit (DDU) 2. outpatient DD clinic 3. specialist inpatient unit 4. general psychiatric ward Outcome data from Gossop *et al.*, 1986	Cost and cost-effectiveness analysis	Costs: were taken from the NTORS study. Cost per week, per episode, per abstinence case were calculated for all four options Cost per abstinence case: £1,636 inpatient, £1,840 outpatient, £12,189 DDU, £6,421 general psychiatric ward Outcomes: successful detoxification completion rates 1.81% inpatient DDU 2.17% outpatient DD clinic 3.75% specialist inpatient unit 4.43% general psychiatric ward	The cost ratio for inpatient compared with outpatient is almost 2:1, adjusted for achievement of abstinence (for 10-day inpatient treatment costs are almost the same). The cost ratio for specialist DDU compared with general psychiatric ward is 1.9:1, adjusted for successful detoxification.	No sensitivity analysis was performed Discounting: not needed since time horizon for all analyses is less than 12 months Crude cost estimations used Internal validity: 4/9/10

Characteristics of reviewed studies: Efficacy of pharmacological interventions

Comparisons Included in this Clinical Question

(Opiate antagonist + anaesthesia) versus pharmacological with minimal sedation
ARNOLDREED2005
COLLINS2005
DEJONG2005
FAVRAT2006
KRABBE2003
MCGREGOR2002
SEOANE1997

Buprenorphine versus adrenergic agonist
CHESKIN1994
JANIRI1994
LING2005
LINTZERIS2002
MARSCH2005
NIGAM1993
OCONNOR1997
PONIZOVSKY2006
RAISTRICK2005
UMBRICHT2003

Buprenorphine versus dihydrocodeine
SHEARD2007
WRIGHT2007A

Buprenorphine versus methadone
JOHNSON1992
PETITJEAN2002
SEIFERT2002
UMBRICHT2003

Buprenorphine versus other pharmacological treatment
JANIRI1994
SCHNEIDER2000

Buprenorphine-naloxone versus adrenergic agonists
LING2005

Clonidine versus lofexidine
CARNWATH1998
GERRA2001
KAHN1997
LIN1997

Clonidine versus opiate antagonists
GERRA1995

Methadone versus (methadone + adrenergic agonist)
GHODSE1994
SAN1994

Methadone versus adrenergic agonist
BEARN1996
GERRA2000
HOWELLS2002
JIANG1993
KLEBER1985
SAN1990
UMBRICHT2003
WASHTON1980

Methadone versus other opiate agonist
SALEHI2006
SORENSEN1982
TENNANT1975
TENNANT1978

Methadone versus other pharmacological treatment
BEARN1996
DRUMMOND1989
HOWELLS2002
JOHNSON1992
KLEBER1985
TENNANT1975

Opiate antagonist versus no opiate antagonist
BESWICK2003A
GERRA1995
GERRA2000
OCONNOR1997
UMBRICHT1999

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ARNOLDREED2005 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Open Duration (days): Range 1-10	n= 80 Age: Mean 30 Range 16-50 Sex: 51 males 29 females Diagnosis: 100% opiate dependence by DSM-IV	**Data Used** Abstinence: 1 month Completion Withdrawal severity	**Group 1 N= 41** Opiate antagonist: naloxone with inpatient - Rapid detoxification: IV naloxone (~800 micrograms) over 5-8 min interspersed with IV clonidine (150 micrograms in 10 ml saline)	Study quality: 1+

Followup: 4 weeks Setting: Perth, Australia Notes: Randomisation: No details reported Info on Screening Process: Not mentioned	Exclusions: - Enrolled in any other opiate treatment research project - Pregnant - Unable to complete study protocol, for example due to pending incarceration - History of adverse reactions to study medications - Medical conditions potentially exacerbated by opiates - Major psychiatric condition that would preclude informed consent Notes: PRIMARY DRUG: Heroin. 6.2% also used other opioids in addition to heroin Baseline: 66% used heroin for >=5 years, 47% daily for >=5 years Past month other substance use: 64% cannabis, 51% alcohol, 45% tranqulisers, 26% amphetamines, 1% cocaine		Opiate antagonist: naltrexone - 20-30 min after IV protocol, oral doses of 4, 8, 15 and 23mg naltrexone at 30 min intervals Symptomatic - Subcutaneous octreotide (0.1mg) and IV ondansetron (2mg) premedication; also oral flunitrazepam depending level of opioid use prior to treatment Midazolam hydrocholride during IV detox protocol depending on level of arousal/discomfort experienced **Group 2 N= 39** Alpha2 adrenergic agonist: clonidine. Mean dose 75-150 micrograms - 75-150 micrograms oral clonidine (reviewed daily), over 5-7 days for inpatient setting or 10 days for outpatient setting Symptomatic - 10-20mg temazepam, additional medications (for example hyosine butylbromide, quinine bisulphate, metacloprimide hydrochloride) at doses indicated for symptomatic relief	
BEARN1996 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design Blindness: Double blind Duration (days): Mean 20 Setting: London, UK Notes: Randomisation procedure not reported Info on Screening Process: 86 referred and enrolled	n= 86 Age: Mean 32 Range 18-62 Sex: 69 males 17 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - major psychiatric or physical illness - pregnant - taking neuroleptic or antidepressant medication Notes: 37/86 were using benzodiazepines at admission Baseline: Years of heroin misuse: 10.5	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 42** Alpha2 adrenergic agonist: lofexidine with inpatient - 0.6 mg per day until day 4, maintained at 2 mg per day for 3 days, then tapered over 3 days Benzodiazepine: diazepam with inpatient - For those also dependent on benzodiazepines: 3 days' stabilisation then tapered over 21 days Placebo - Placebo syrup **Group 2 N= 44** Opiate agonist: methadone with inpatient - Variable initial dose, tapered over 10 days at a linear rate Placebo - Placebo tablet Benzodiazepine: diazepam with inpatient - For those also dependent on benzodiazepines: 3 days' stabilisation then tapered over 21 days	Both groups underwent 3-day stabilisation period during which methadone dose was titrated to subjective and observed opiate withdrawal symptoms Study quality 1+
BESWICK2003A Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol for follow-up analyses Blindness: Double blind Duration (days): Mean 6 Followup: 6 months Setting: Specialist drug dependency units in London Info on Screening Process: 220 invited; 91 randomised and 46 assigned to methadone group	n= 91 Age: Mean 32 Range 18-56 Sex: 105 males 32 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - on >100 mg MMT - history of epilepsy - severe liver disease - pregnancy - psychotropic medication - alcohol dependence Notes: ETHNICITY: 89% White Baseline: 'No differences between the randomised groups' - but did not make clear what differences there might have	**Data Used** Opiate use Relapse Abstinence: 1 month Completion Notes: DROPOUTS: 27% lofexidine + naloxone, 22% lofexidine + placebo	**Group 1 N= 45** Alpha2 adrenergic agonist: lofexidine with inpatient: drug dependence unit (DDU) - As described in Bearn (1996): 1.8 mg in three divided doses on day 1, 1 mg twice daily for 3 days, then 0.6 mg twice daily on days 5-6. Additional 0.4 mg available during any 24-hour period on patient request Opiate antagonist: naloxone. Mean dose 0.8 mg - 0.8 mg naloxone solution days 3 6	Patients who refused randomisation or met exclusion criteria were retained in a non-randomised methadone control group (not described here) Study quality: 1+

	been		**Group 2 N= 46** Alpha2 adrenergic agonist: lofexidine with inpatient: drug dependence unit (DDU) - As described in Bearn (1998): 1.8 mg in three divided doses on day 1, 1 mg twice daily for 3 days, then 0.6 mg twice daily on days 5-6. Additional 0.4 mg available during any 24-hour period on patient request. Placebo - Placebo solution days 3-6	
CARNWATH1998 Study Type: RCT (randomised controlled trial) Study Description: Drugs prepared in identical capsules Blindness: Double blind Duration (days): Mean 28 Notes: RANDOMISATION: By pharmacy	n= 50 Age: Mean 28 Sex: 35 males 15 females Diagnosis: 100% opiate misuse Exclusions: Not stabilised on <=40 mg per day methadone Notes: PRIMARY DIAGNOSIS: Users of methadone or other opiates Baseline: (GROUPS: lofexidine / clonidine) Previous detoxification experience: 57% / 75% Employed: 17% / 17%	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Withdrawal severity Completion	**Group 1 N= 26** Alpha2 adrenergic agonist: lofexidine. Mean dose 0.2 mg - 0.2 mg per capsule, increased to max 8 capsules per day over 3 days, tapered over last 3 days. Duration of medication unclear **Group 2 N= 24** Alpha2 adrenergic agonist: clonidine - As per lofexidine except with 0.1 mg clonidine capsules	Study quality 1+
CHESKIN1994 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 10 Followup: 8 day placebo/follow-up phase Setting: US closed research ward Notes: Randomisation stratified on Clinical Institute Narcotics Assessment (CINA) score	n= 25 Age: Range 21-45 Sex: 9 males 16 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - not presenting three consecutive non-methadone, opiate-positive urines - self-reported history inconsistent with opiate addiction, or lack of fresh needle marks - participation in structured buprenorphine or clonidine research programme in past 12 months - ASI psychiatric score >=7 - active psychosis or schizophrenia - active cardiovascular or hepatic disease - used methadone >7 days in past 4 months - sitting systolic BP <110 mmHg or diastolic <70 mmHg - reported hypersensitivity to study medications Notes: Reported baseline data are for completers only Baseline: GROUPS: clonidine / buprenorphine CINA score: 33.2 / 30.1 Years of opiate use: 12.6 / 10.7	**Data Used** Withdrawal severity Completion	**Group 1 N= 13** Alpha2 adrenergic agonist: clonidine with inpatient - Total 2.7 mg oral in divided doses, three times daily over 3 days Placebo - 1 ml sublingual solution three times daily for 18 days **Group 2 N= 12** Opiate partial agonist: buprenorphine with inpatient. Mean dose 17 mg - Total 17 mg sublingual in divided doses, three times daily over 3 days Placebo - Oral placebo capsule three times daily for 18 days	Additional symptomatic medications available for specific symptoms, but were not requested by any participant throughout study Study quality 1++
COLLINS2005 Study Type: RCT (randomised controlled trial) Study Description: Patients not blinded Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 84 Setting: US	n= 106 Age: Mean 36 Range 21-50 Sex: 76 males 30 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age outside 21-50 range	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Completion Retention: duration in treatment	**Group 1 N= 37** Opiate partial agonist: buprenorphine with inpatient. Mean dose 8 mg - Single sublingual dose on evening of day 1 Symptomatic with inpatient - As needed	Study quality: 1++

3 days' inpatient phase followed by 12 weeks' outpatient phase Notes: RANDOMISATION: Blocks of 12 with computer-generated assignments ALLOCATION: Staff remained unaware of randomisation sequence Info on Screening Process: 169 screened; 35 met exclusion criteria and 28 lost to follow-up or refused consent; 106 enrolled and randomised	- poor general health or acute medical illness - DSM-IV criteria for dependence on alcohol or non-opiate drugs - pregnancy or lactation or failure to use adequate birth control - history of significant violent behaviour - schizophrenia and/or major mood disorder - suicide risk - current psychotropic medication, MAO inhibitors, protease inhibitors - positive cocaine urinalysis on admission - BMI > 40 - Blood glucose concentration > 160 mg/L - history of food or drug allergy, sensitivity to study medication Notes: PRIMARY DIAGNOSIS: Opiate dependence >=6 months and seeking treatment ETHNICITY: 53% White Baseline: (GROUPS: ultrarapid / buprenorphine / clonidine) Heroin use (days in past 30): 30 / 29 / 29 Lifetime heroin use disorder (years): 7.6 / 7.4 / 6.4 Previous inpatient detoxification attempts: 1.74 / 1.59 / 1.21 Previous inpatient rehabilitation attempts: 0.57 / 0.54 / 0.56 Previous outpatient detoxification attempts: 0.17 / 0.11 / 0.29 Previous MMT: 0.66 / 0.57 / 0.53		Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Opiate antagonist: naltrexone with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days Alpha2 adrenergic agonist: clonidine with inpatient - As needed **Group 2 N= 34** Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Opiate antagonist: naltrexone with outpatient - Initial 12.5 mg dose on day 6, followed by 25 mg next day and 50 mg maintenance dose on subsequent days Alpha2 adrenergic agonist: clonidine with inpatient - As needed **Group 3 N= 35** Symptomatic with inpatient - As required: clonazepam, up to 2 mg every 8 hours; ketorolac, 30 mg intramuscularly every 6 hours; ondansetron, 8 mg orally every 8 hours or prochlorperazine, 10 mg orally/intramuscularly every 8 hours; octreotide, 100 mcg every 8 hours; and so on Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Anaesthetic: propofol with inpatient - 25-150 mcg/kg per min; anaesthesia maintained for 2-4 hours Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - Induced on 50 mg then maintained throughout outpatient phase Alpha2 adrenergic agonist: clonidine with inpatient - As needed, up to 0.2 mg every 4 hours (max 1.2 mg/day)	
DEJONG2005 Study Type: RCT (randomised controlled trial) Study Description: 7 days' inpatient treatment followed by 10 months' outpatient community reinforcement approach	n= 272 Age: Mean 36 Sex: 223 males 49 females	**Data Used** Withdrawal: Subjective Opiate Withdrawal Scale Urinalysis	**Group 1 N= 137** Symptomatic with inpatient - As per ultrarapid group	Study quality: 1++

Blindness: Open Duration (days): Mean 300 Setting: Four addiction treatment centres in the Netherlands Notes: RANDOMISATION: Centralised and computerised, in blocks of two Info on Screening Process: 296 screened, 24 met exclusion criteria or refused consent; 272 enrolled and randomised	Diagnosis: opiate dependence by DSM-IV Exclusions: - age <18 - no previous unsuccessful detox attempts - lack of a non-opiate user in social network - severe somatic or psychiatric disorders - pregnancy - AIDS - contraindications to general anaesthesia - cocaine use in past 48 hours Baseline: (GROUPS: ultrarapid / no anaesthesia) Years of heroin use: 12.0 / 12.1 Age first heroin use: 20.9 / 20.8 Previous detoxification attempts: 7.4 / 8.4 Heroin use past 30 days: 18.0 / 18.8 Methadone use past 30 days: 22.0 / 23.6	Opiate use Withdrawal: COWS (Clinical Opiate Withdrawal) Abstinence: 1 month	Psychosocial: CRA (community reinforcement apprch) with outpatient - As per ultrarapid group Opiate antagonist: naltrexone with inpatient - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Alpha2 adrenergic agonist: clonidine with inpatient - As per ultrarapid group **Group 2 N= 135** Symptomatic with inpatient - All participants treated with same medications at same dosages: 8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotride, ondansetron, butylscopolamine, diazepam; haloperidol and midazolam as necessary Anaesthetic: propofol with inpatient. Mean dose 5000 ng/ml - Anaesthesia induced on first signs of opiate withdrawal, using target controlled infusion method, and maintained for 4 hours Psychosocial: CRA (community reinforcement apprch) with outpatient - 23 sessions over 10 months: 10 monitoring naltrexone compliance, addictive behaviours and craving; 13 working on drug-refusal behaviour, relational issues, problem solving, social skills training and craving management with accompanying non drug user Opiate antagonist: naltrexone with inpatient - Administered at 9 am to precipitate withdrawal. At the end of anaesthesia, 100 mg administered through orogastric tube. Continued on maintenance dose (50 mg) for 10 months Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.3 mg - Administered at 9 am to prevent high blood pressure Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day	
DRUMMOND1989 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 14 Setting: Inpatient detoxification at three Glasgow hospitals Notes: RANDOMISATION: Participants randomly assigned to one of two groups. Pharmacy department disguised preparations. Info on Screening Process: 33 screened, 9 excluded, 24 met inclusion criteria	n= 24 Age: Mean 25 Sex: 13 males 11 females Diagnosis: 85% opiate dependence by urinalysis Notes: Primary drug: heroin 3 participants took benzodiazepine on a regular basis 13 participants reported occasional use of cannabis Baseline: Mean duration of drug use: 4.7 years (SD = 2.2) Mean daily dose of heroin 0.8 g (SD = 0.6)	**Data Used** Urinalysis Withdrawal: Subjective Opiate Withdrawal Scale Withdrawal: OOWS (Objective Opiate Withdrawal)	**Group 1 N= 13** Opiate agonist: methadone with inpatient. Mean dose 20 mg - Participants received methadone linctus 20 mg orally in the first 24 hours and placebo tablets together. Thereafter they could receive 30 mg more if needed **Group 2 N= 11** Benzodiazepine: chlordiazepoxide with inpatient. Mean dose 200 mg - Patients received 200 mg of chlordiazepoxide orally in the first 24 hours with the option of a further 300 mg if needed	Study quality 1+
FAVRAT2006				

Study Type: RCT (randomised controlled trial) Study Description: Randomisation by pharmacist Type of Analysis: ITT Blindness: No mention Duration (days): Range 1-7 Setting: Switzerland Notes: RANDOMISATION: Computer-generated numbers Info on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised	n= 70 Age: Mean 30 Sex: 54 males 16 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age <18 - alcohol, cocaine or benzodiazepine dependence, or positive urinalysis prior to starting treatment - pregnancy - known idiosyncratic reactions - severe psychiatric comorbidity - other serious medical conditions Baseline: (Ultra-rapid / clonidine) ASI (drug): 0.34 / 0.35	**Data Used** ASI (Addiction Severity Index) Completion Abstinence: 12 months Abstinence: 3 months Notes: Completion defined as 3 days of retentior in treatment for anaesthesia without drug consumption and 7 days for clonidine FOLLOW-UPS: At 3, 6 and 12 months	**Group 1 N= 34** Psychosocial: individual therapy with outpatient - As per ultrarapid group Symptomatic with inpatient - Limited to one drug at one dosage per indication: loperamide 4 mg, tolperisone 150 mg, ondansetron 4 mg, zolpidem 10 mg, olanzapine 5 mg, paracetamol 500 mg Alpha2 adrenergic agonist: clonidine with inpatient - 0.600 mg/day for first 3 days, 0.300 mg on day 4, 0.225 mg on day 5, 0.150 mg on day 6 and 0.075 mg on day 7 (in divided 0.075 mg doses) **Group 2 N= 36** Psychosocial: individual therapy with outpatient - One week of "intensive" psychosocial support following discharge Symptomatic with inpatient - During anaesthesia, octreotide. After anaesthesia, during recovery phase: 30 mg intravenous ketorolac, glycopyrrolate if needed and 5 mg droperidol for delirium if needed. Anaesthetic: propofol with inpatient - Monitored and maintained at bispectral index 45-60 by propofol infusion (around 5-6 hours) Opiate antagonist: naltrexone with inpatient. Mean dose 100 mg - Oral, with 30 mg oral sodium citrate to precipitate withdrawal. Before leaving ICU, 24 hours after start of treatment, initiation of maintenance dose (50 mg) oral naltrexon Alpha2 adrenergic agonist: clonidine with inpatient - During anaesthesia, clonidine or lidocaine used to deepen anaesthesia and control withdrawal signs	Study quality: 1++
GERRA1995 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 4 Followup: 3 and 6 months Setting: Italy Notes: Randomisation procedure not described	n= 152 Age: Range 18-32 Sex: 125 males 27 females Diagnosis: 100% opiate misuse by DSM-III-R Exclusions: - cirrhosis - psychiatric symptoms (Minnesota Multiphasic Personality Inventory [MMPI]) - immune system depression Notes: PRIMARY DIAGNOSIS: Abused heroin for 24-48 months Baseline: None reported	**Data Used** Withdrawal severity Urinalysis Completion Notes: DROPOUTS: 2/33 clonidine, 2/42 clonidine-naltrexone, 1/58 clonidine-naloxone, 5/19 placebo	**Group 1 N= 33** Psychosocial: individual therapy - Psychotherapy - no further details Placebo with outpatient - Placebo tablets for 3 months Alpha2 adrenergic agonist: clonidine with outpatient. Mean dose 0.15 mg - Intravenous clonidine three times daily for 4 days **Group 2 N= 42** Psychosocial: individual therapy - Psychotherapy -- no further details Opiate antagonist: naltrexone with outpatient. Mean dose 50 mg - daily beginning on day 2. Maintained on naltrexone for following 3 months. Alpha2 adrenergic agonist: clonidine with outpatient - As per clonidine group	Study quality 1+

			Group 3 N= 58 Psychosocial: individual therapy - Psychotherapy -- no further details Opiate antagonist: naloxone with outpatient - 0.2 mg intravenous naloxone on day 2, 0.4 mg twice daily over next 2 days Placebo with outpatient - Orally from day Opiate antagonist: naltrexone with outpatient. Mean dose 50 mg - Maintained from day 2 for 3 months Alpha2 adrenergic agonist: clonidine with outpatient - As per clonidine group **Group 4 N= 19** Psychosocial: individual therapy - Psychotherapy -- no further details Placebo with outpatient - Intravenous saline for 4 days, and oral placebo from day 2 for 3 months	
GERRA2000 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 10 Followup: 6 months Setting: Italy	n= 98 Age: Range 18-36 Sex: 71 males 27 females Diagnosis: 100% opiate dependence by DSM-III-R 100% opiate misuse by DSM-IV Exclusions: - polydrug dependence or prolonged use of drugs other than heroin - severe chronic liver, renal or other physical disorders - psychosis - recent weight loss or obesity - endocrinopathies - immunodeficiencies Notes: PRIMARY DIAGNOSIS confirmed by urinalysis Baseline: Years of heroin use: 2-6	**Data Used** Entry to further treatment: naltrexone maintenance Withdrawal severity Opiate use	**Group 1 N= 32** Alpha2 adrenergic agonist: clonidine with outpatient - Intravenous clonidine 0.15 mg in 100 mL saline three times in the morning and afternoon for 2 days; in following 3 days half doses of clonidine administered (0.15 mg 3 times a day). At 11pm clonidine orally received every evening for 5 days **Group 2 N= 32** Opiate antagonist: naltrexone with outpatient - Naloxone injections until full dose of 0.04 mg reached. Naltrexone syrup 5 mg orally on day 1, 50 mg on day 2 Alpha2 adrenergic agonist: clonidine with outpatient - As per clonidine group (group 1) Symptomatic - 60 mg oxazepam twice a day, 10 mg oral baclofen twice a day, 400 mg ketoprofene twice a day **Group 3 N= 34** Opiate agonist: methadone with inpatient - Dose tapered from 40 mg to 0 mg in 10 days, adminstered once daily in syrup	Intravenous heroin administered to all participants until 12 hours before treatment All participants admitted to naltrexone maintenance post treatment Study quality 1+
GERRA2001 Study Type: RCT (randomised controlled trial) Blindness: Single blind Duration (days): Mean 3 Setting: Italy Info on Screening Process: All those asked gave consent and were randomised	n= 40 Age: Range 20-32 Sex: all males Diagnosis: 100% opiate dependence Exclusions: - female - heavy polydrug misuse: long-lasting consumption of alcohol or other drugs - psychosis - severe chronic liver illness	**Data Used** Withdrawal severity Urinalysis Completion Notes: DROPOUTS: clonidine 15%, lofexidine 10%	**Group 1 N= 20** Alpha2 adrenergic agonist: lofexidine - 0.2 mg tablets three times in the morning and three times in the afternoon for 3 days. On day 2, additional tablet at 9pm and at 12pm. Benzodiazepine: oxazepam. Mean dose 60 mg - Orally, twice a day GABA agonist: baclofen - 10 mg orally three times daily Ketoprofene. Mean dose 400 mg - 400 mg intravenous daily, in 1000 ml saline	Study quality 1+

	- renal disease - other chronic medical disorders - recent significant weight loss or obesity - endocrinopathy - immunodeficiency Notes: PRIMARY DIAGNOSIS: Heroin Baseline: Heroin use: 3-6 years, 1.5-2.0 g street heroin daily		**Group 2 N= 20** Benzodiazepine: oxazepam. Mean dose 60 mg - Orally, twice per day GABA agonist: baclofen. Mean dose 10 mg - 10 mg orally 3 times daily Ketoprofene. Mean dose 400 mg - 400 mg intravenous daily, in 1000 ml saline Alpha2 adrenergic agonist: clonidine with outpatient. Mean dose 0.15 mg - 0.15 mg tablets 3 times in the morning and 3 times in the afternoon for 3 days. On day 2, additional tablet at 9pm and at 12pm.	
GHODSE1994 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 14 Followup: 4 weeks Setting: Drug dependency unit in UK	n= 86 Age: Range 18-47 Sex: 59 males 27 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT Exclusions: Cardiovascular or other disorder which might contraindicate clonidine Notes: PRIMARY DIAGNOSIS: Receiving a stable regime of MMT	**Data Used** Withdrawal severity Completion Notes: DROPOUTS: 18/42 clonidine, 14/44 placebo failed to complete detoxification	**Group 1 N= 42** Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0 Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.1 mg tablets - Divided doses, initially 0.2 mg daily, increasing by 0.1 mg daily until maximum tolerated dose or 1.2 mg reached. Dose reduced by 0.1 mg if a blood pressure reading < 90/60 mm Hg recorded. **Group 2 N= 44** Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0 Placebo with inpatient - Administered identically to clonidine	Study quality 1+
HOWELLS2002 Study Type: RCT (randomised controlled trial) Study Description: Allocation by pharmacist, who oversaw blinding procedures throughout study; double dummy design Type of Analysis: ITT Blindness: Double blind Duration (days): Mean 10 Setting: UK male prison Notes: RANDOMISATION: 'Simple randomisation procedure' by pharmacist Info on Screening Process: 76 eligible, 2 withdrew consent and so 74 randomised. 6 mistakenly entered for detoxification twice; 68 included in analysis.	n= 68 Age: Mean 31 Range 22-49 Sex: all males Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age >=55 - serious psychiatric (including psychotic depression and schizophrenia) or physical illness Notes: PRIMARY DIAGNOSIS: Opiate use confirmed by urinalysis Baseline: GROUPS: methadone / lofexidine Years from first use of heroin: 9.5 / 8.8 Use of other drugs in past month: benzodiazepines 68%, amphetamine 5%, non-prescribed methadone 5%, cocaine 1%, crack cocaine 2%	**Data Used** Withdrawal: WPS (Withdrawal Problems Scale) Withdrawal: Short Opiate Withdrawal Scale SDS (Severity of Dependence Scale) Withdrawal severity Completion	**Group 1 N= 36** Opiate agonist: methadone with prison - 30 mg day 1, 25 mg days 2-3, 20 mg days 4-5, tapered to 0 in 10 days Placebo - Placebo peach coloured tablets, twice daily for 10 days **Group 2 N= 32** Alpha2 adrenergic agonist: lofexidine with prison - 0.6 mg day 1, increased by 0.4 mg per day until day 4, 2 mg per day for 3 days, next 3 days tapered by 0.4 mg per day Placebo - Placebo green syrup, twice daily for 10 days	Study quality 1++
JANIRI1994 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 6 Setting: Italy Notes: RANDOMISATION: not reported	n= 39 Age: Mean 26 Sex: 23 males 16 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - polydrug use	**Data Used** Completion	**Group 1 N= 13** Opiate partial agonist: buprenorphine with inpatient - Intramuscularly: 0.9 mg days 1 and 2, 0.45 mg day 3, 0.15 mg day 4 **Group 2 N= 13** Alpha2 adrenergic agonist: clonidine with inpatient - Intramuscularly: 0.3-0.9 mg per day for 6 days	Study quality 1+

	- not been on MMT for >=1 year - severe complicating medical conditions, or psychiatric disorders impairing volition and reality testing - body weight abnormalities - not highly motivated toward abstinence Notes: PRIMARY DRUG: 17/39 participants were using heroin on top of methadone Baseline: Mean duration of opiate dependence = 7.5 (3.6) years, duration in MMT = 3.4 (2.4) years 41% HIV+		**Group 3 N= 13** Lefetamine with inpatient - Intramuscularly: 60-240 mg per day for 6 days	
JIANG1993 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 12 Setting: Five rehabilitation centres in China Notes: RANDOMISATION: No details	n= 200 Age: Mean 25 Sex: 155 males 45 females Diagnosis: opiate dependence by DSM-III-R Exclusions: Concurrent medical conditions, infectious diseases or mental illness Notes: REFERRALS: Not all participants entered voluntarily Baseline: GROUPS: Methadone / clonidine Using orally only: 80% / 67%	**Data Used** Withdrawal severity Hamilton Anxiety Rating Scale Notes: DROPOUTS: None reported Withdrawal outcomes were observer-rated; not extracted	**Group 1 N= 100** Opiate agonist: methadone with outpatient. Mean dose max 21.6 mg - Max dose on days 1-2, then tapered and ceased after day 12; dose titrated against withdrawal and side effects **Group 2 N= 100** Alpha2 adrenergic agonist: clonidine with inpatient - 'Sufficient' dose days 1-4, tapered days 5-8, ceased after day 11; dose titrated against withdrawal and side effects	Report in Chinese; data extracted by Ryan Li Study quality 1+
JOHNSON1992 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 180 Setting: US	n= 162 Age: Mean 33 Sex: 113 males 49 females Diagnosis: Exclusions: - <21 or >50 years of age - self-reported duration <4 months - <2 episodes of heroin use per day - self-reported daily value of use <$50 per day - <4 on self-reported level of withdrawal on a 9-point scale 12 hours after last heroin dose - <2/3 urine samples positive for opiates (not including methadone) - severe psychiatric condition Baseline: GROUPS: Buprenorphine (8 mg / day)/ methadone (20 mg / day) / methadone (60 mg / day) Months of addiction: 31.0 (11.2) / 31.5 (10.8) / 30.2 (9.6) $ / day opioid use: 114.1 (91.7) / 115.3 (65.3) / 106.2 (49.9)	**Data Used** Completion Abstinence: endpoint Notes: DROPOUTS: Buprenorphine = 70%, methadone 60 mg = 80%, methadone 20 mg = 94% Abstinence assessed by total number of negativ urine samples -- not used	**Group 1 N= 54** Opiate agonist: methadone with outpatient - Maintained on 60 mg methadone for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study **Group 2 N= 53** Opiate partial agonist: buprenorphine with outpatient - Maintained on 6 mg buprenorphine for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study **Group 3 N= 55** Opiate agonist: methadone with outpatient - Maintained on 20 mg methadone for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study	No discussion of whether opiate dependent Study quality 1+
KAHN1997 Study Type: RCT (randomised controlled trial) Study Description: Patients blind to methadone cessation on day 3 Blindness: Double blind Duration (days): Mean 18	n= 28 Age: No information Sex: 19 males 9 females Diagnosis: 100% opiate dependence Exclusions: - not stabilised on methadone 3-4 days prior to study	**Data Used** Withdrawal severity	**Group 1 N= 14** Alpha2 adrenergic agonist: lofexidine - 0.4 mg rising to max 1.8 mg per day, tapered over days 15-18; lorazepam as adjunct as appropriate Opiate agonist: methadone - Substituted with placebo on day 3; placebo stopped on day 14	Study quality 1+

	- alcohol dependence Notes: PRIMARY DIAGNOSIS: by history and urine screen		**Group 2 N= 14** Opiate agonist: methadone - Substituted with placebo on day 3; placebo stopped on day 14 Alpha2 adrenergic agonist: clonidine - 0.2 mg rising to max 0.9 mg per day, tapered over days 15-18; lorazepam as adjunct as appropriate	
KLEBER1985 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design; blinding of nurse who administered withdrawal rating scale, and physician who provided psychological support Blindness: Single blind Duration (days): Mean 30 Setting: Component of multicentre study in USA Notes: RANDOMISATION: No details	n= 49 Age: Mean 29 Sex: 37 males 12 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT Exclusions: - age outside range 21-50 - current use of MAO inhibitors, neuroleptics, sedatives or other antihypertensive drugs (except diuretics) - current alcohol abuse - history of allergy to imidazolidone drugs - any medical or psychiatric illness that would subject patient to unnecessary risk or compromise objective evaluation of the investigative drug (e.g. cardiac disorders, renal disorders, hypertension, schizophrenia, severe affective disorders) - pregnancy Notes: PRIMARY DIAGNOSIS: Receiving methadone <=20 mg per day for >=6 months ETHNICITY: 71% White Baseline: Length of addiction: 10 years	**Data Used** ASI (Addiction Severity Index) Withdrawal severity BDI (Beck Depression Inventory) Completion	**Group 1 N= 25** Opiate agonist: methadone with outpatient - Initial dose 20 mg per day, single daily oral dose tapered by 1 mg per day; choral hydrate 0.5-1 g permitted as an adjunct for insomnia Placebo - Methadone placebo from days 21-30; clonidine placebo tablets throughout study **Group 2 N= 24** Alpha2 adrenergic agonist: clonidine with outpatient - Initial dose 0.3 mg per day in three divided doses, gradual increase to max 1 mg per day by day 6; tapered by 20-25% per day from day 11. Choral hydrate 0.5-1 g permitted as an adjunct for insomnia. Placebo - Clonidine placebo tablets from days 16-30; methadone placebo syrup throughout study	Study quality 1+
KRABBE2003 Study Type: Non-randomised controlled trial Type of Analysis: ITT (dropouts treated as nonabstinent) Blindness: Open Duration (days): Range 4-20 Followup: 3 months Setting: Hospital in the Netherlands Notes: RANDOMISATION: Consecutive assignment (first 15 to ultrarapid group) - potential bias Info on Screening Process: 30 enrolled	n= 30 Age: Mean 33 Sex: 24 males 6 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - Age outside range 18-40 - No documented failed efforts of standard methadone tapering - No definite desire for sustained abstinence - Dependent on other drugs - Severe physical illness contraindicating general anaesthesia - Pregnancy Baseline: (GROUPS: Ultrarapid / Methadone) Years of heroin use: 11.1 / 6.3 Years of methadone use: 9.4 / 3.5 Methadone dose (mg/day): 58.4 / 38.5 Number of previous treatments: 9.6 / 6.9	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Abstinence: 1 month Completion Abstinence: 3 months Notes: FOLLOWUPS: Monthly for 3 months DROPOUTS: 60% methadone, 0% ultrarapid	**Group 1 N= 15** Opiate agonist: methadone with inpatient - Tapered to 0 in 1-2 weeks Opiate antagonist: naltrexone with outpatient - Approx. 6 days after last dose of methadone, 50mg maintenance dose administered daily under supervision **Group 2 N= 15** Symptomatic - Range of adjunct medications after 2nd naltrexone dose (e.g. anti-emetics, anti-diuretics, clonidine Anaesthetic: propofol with inpatient - Naltrexone 100mg oral + 5mg tropisetron IV. Propofol anaesthesia induced when withdrawal evident. Mechanical ventilation. 0.8mg naloxone test every 20 min until no withdrawal, then 100mg naltrexone via nasogastric tube. Opiate antagonist: naltrexone with outpatient. Mean dose 50mg - After discharge, maintenance dose given for 3 months	
LIN1997				

Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 9 Setting: Taiwan Notes: RANDOMISATION: No details	n= 80 Age: Mean 32 Sex: 65 males 15 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: None specified Notes: PRIMARY DIAGNOSIS: Street heroin ETHNICITY: Chinese Baseline: Years of heroin use: 4.2 lofexidine / 4.6 clonidine Estimated pure heroin used daily, mg: 315 Administration route: 88% injection, 12% smoking Using methamphetamine: 14/80	**Data Used** Withdrawal severity Retention: duration in treatment	**Group 1 N= 40** Alpha2 adrenergic agonist: lofexidine with inpatient. Mean dose 0.2 mg capsules - four times a day on day 1, then titrated dependent on withdrawal symptoms and blood pressure. Dose held steady for next 2 days, then tapered to 0 over the next 2-4 days. Max dose never exceeded 8 capsules per day **Group 2 N= 40** Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.075 mg - 4 times a day on day 1, then titrated dependent on withdrawal symptoms and blood pressure. Dose held steady for next 2 days, then tapered to 0 over the next 2-4 days. Max dose never exceeded eight capsules per day	Study quality 1+
LING2005 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 13 Setting: Six inpatient and six outpatient community-based treatment programmes in US	n= 344 Age: Mean 38 Sex: 234 males 110 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - <18 years - serious medical or psychiatric condition - allergy or sensitivity to study medications - pregnancy Baseline: Years of use: inpatient sample = 9, outpatient sample = 7	**Data Used** Withdrawal: COWS (Clinical Opiate Withdrawal) Completion	**Group 1 N= 77** Opiate partial agonist: buprenorphine-naloxone with inpatient - Sublingually: 8 mg buprenorphine/2 mg naloxone day 1, increasing in stepwise manner to 16 mg buprenorphine/4 mg naloxone day 3, and tapering to 2 mg buprenorphine/0.05 mg naloxone by days 12/13 **Group 2 N= 157** Opiate partial agonist: buprenorphine-naloxone with outpatient - Sublingually: 8 mg buprenorphine/2 mg naloxone day 1, increasing in stepwise manner to 16 mg buprenorphine/4 mg naloxone day 3, and tapering to 2 mg buprenorphine/0.05 mg naloxone by days 12/13 **Group 3 N= 74** Alpha2 adrenergic agonist: clonidine with outpatient - Oral & transdermal patch: 0.05-0.1mg every 6 hrs day 1 (not exceeding 0.6mg in total), if oral dose well tolerated clonidine transdermal patch given for 7 days, oral clonidine discontinued on day 7, new patch delivered on day 7 and discontinued on day 13 **Group 4 N= 36** Alpha2 adrenergic agonist: clonidine with inpatient - Oral & transdermal patch: 0.05 0.1mg every 6 hrs day 1 (not exceeding 0.6 mg in total), if oral dose well tolerated clonidine transdermal patch given for 7 days, oral clonidine discontinued on day 3, new patch delivered on day 7 and discontinued on day 13	Study quality 1+
LINTZERIS2002 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 8 Followup: 4 weeks	n= 114 Age: Mean 30 Sex: 74 males 40 females Diagnosis: 100% opiate dependence by DSM-IV	**Data Used** Entry to further treatment: naltrexone maintenance Withdrawal: Short Opiate Withdrawal Scale Opiate use Completion	**Group 1 N= 58** Opiate partial agonist: buprenorphine with outpatient. Mean dose 6 mg / day - Supervised single daily dose of sublingua tablet, adjusted to symptoms and ceased on day 5	Both groups received counselling during treatment, naltrexone or counselling offered as aftercare Study quality 1++

Setting: Australia, two specialist outpatient centres Notes: RANDOMISATION: By an independent organisation Info on Screening Process: 272 screened; 85 excluded and 45 chose not to participate.	Exclusions: - <18 years - opiate-negative urine at screening - MMT for last 8 weeks - significant medical or psychiatric conditions - concurrent alcohol, benzodiazepine, amphetamine, cocaine dependence - homeless - pregnant Baseline: GROUPS: Buprenorphine / clonidine No. days' use in 28: 26.3 (2.9) / 25.3 (4.5) Average daily cost in $AUS 95.90 (71.80) / 100.60 (74.20)	Notes: DROPOUTS: Buprenorphine = 8/58, clonidine = 32/56	**Group 2 N= 56** Alpha2 adrenergic agonist: clonidine with outpatient. Mean dose 500 mcg / day - 100-150 mcg four times a day as required, plus symptomatic medications	
MARSCH2005 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 28 Setting: US	n= 36 Age: Mean 17 Range 13-18 Sex: 14 males 22 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - pregnancy - active significant psychiatric disorder - significant medical illness (e.g. cardiovascular) Notes: Adolescent sample Baseline: GROUPS: Buprenorphine / clonidine Days' use in last 30: 27.7 (3.0) / 27.7 (4.8)	**Data Used** Completion Abstinence: endpoint Notes: Abstinence measured as number of negative urine samples -- not used	**Group 1 N= 18** Opiate partial agonist: buprenorphine with outpatient - Sublingually: <70 kg and 1-3 bags of heroin starting dose 6 mg, >=70 kg and >3 bags of heroin starting dose 8 mg day 1. Buprenorphine reduced by 2 mg every 7 days. All participants received four tablets daily. Placebo with outpatient - Placebo clonidine patches throughout the study which paralleled timeline administration of active clonidine patches in clonidine group **Group 2 N= 18** Placebo with outpatient - All received placebo buprenorphine tablets throughout study paralled timeline of administrationof active buprenorphine doses in the buprenorphine group Alpha2 adrenergic agonist: clonidine with outpatient - Transdermal patches: single patch 0.1 mg day 1, second patch of 0.1 mg added on day 2 worn for days 2-6, optional third patch added for days 4-6. All patches replaced with 0.2 mg dose, day 14 replaced with 0.1 mg, day 21 replaced with 0 mg (placebo patch)	All participants were offered CM and community reinforcement approach (CRA) Study quality: 1++
MCGREGOR2002 Study Type: RCT (randomised controlled trial) Study Description: 3 days' inpatient detoxification procedure followed by 9 months' naltrexone maintenance plus psychosocial intervention Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 270 Followup: 3 months Setting: Two public substance misuse treatment facilities and one teaching hospital in Australia Notes: RANDOMISATION: In blocks of four by research team member blind to participants' identity or history Info on Screening Process: 162 telephone interviewed, 119 screened and 107 enrolled. 6 in pilot group so 101 randomised.	n= 101 Age: Mean 31 Sex: 61 males 40 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - unable to provide details of contact person - currently enrolled in other research - MMT in past 3 months - pregnant, lactating or planning to become pregnant over next 12 months - contraindications to naltrexone - HIV+ - history of adverse events with study medications - medical conditions potentially exacerbated by heroin withdrawal Notes: PRIMARY DIAGNOSIS: Heroin Baseline: GROUPS: Clonidine / ultrarapid Mean severity of dependence: 11.5 / 11.7 Mean age at first heroin use: 21.2 / 21.3	**Data Used** Entry to further treatment: naltrexone maintenance Hair analysis Opiate use Completion Retention: duration in treatment Notes: Completion defined as absence of withdrawal syndrome (Objective Opiate Withdrawal Scale [OOWS] <=4)	**Group 1 N= 50** Psychosocial: individual therapy with outpatient - For 9 months following hospital discharge: monthly naltrexone dispensing and counselling (based on motivational enhancement therapy [MET] and CBT principles) Opiate antagonist: naloxone with inpatient. Mean dose total 10 or 12 mg - Intravenous naloxone administered in four or five bolus doses at 30-min intervals Symptomatic with inpatient - Octreotide for relieving gastrointestinal withdrawal Anaesthetic: propofol with inpatient - Maintained for 4 hours Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - When OOWS <=5 following anaesthesia and naloxone challenge, 50 mg naltrexone given orally	Study quality 1++

	Mean years of heroin use: 9.7 / 10.2 Mean frequency of heroin use in past month: 87.4 / 86.8		Alpha2 adrenergic agonist: clonidine with inpatient **Group 2 N= 50** Psychosocial: individual therapy with outpatient - For 9 months following hospital discharge: monthy naltrexone dispensing and counselling (based on METand CBT principles) Symptomatic with inpatient - Following standard clinical practice: included diazepam, orphenadrine, paracetamol, temazepam, naproxen, metoclopramide, buscopan and vitamins Alpha2 adrenergic agonist: clonidine with inpatient - Following standard clinical practice	
NIGAM1993 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 10 Setting: India Notes: RANDOMISATION: Method not reported	n= 44 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: Polydrug use Baseline: Duration of heroin use = 4-5 years	**Data Used** Withdrawal: Subjective Opiate Withdrawal Scale Completion	**Group 1 N= 22** Alpha2 adrenergic agonist: clonidine with inpatient - Oral: initial dose 0.3 mg / day with maximum of 0.9 mg / day in three divided doses. Nitrazepam as adjunct medication **Group 2 N= 22** Opiate partial agonist: buprenorphine with inpatient - Sublingual tablet: initial dose 0.6 mg / day with maximum 1.2 mg / day in 3 divided doses. Nitrazepam as adjunct medication	Heroin users = 90%, opium users = 10% Study quality 1+
OCONNOR1997 Study Type: RCT (randomised controlled trial) Study Description: Triple dummy design Blindness: Double blind Duration (days): Mean 8 Setting: Primary care clinic, USA Info on Screening Process: 202 screened, 177 eligible. 15 failed to attend on day 1, so 162 randomised	n= 162 Age: Range 18-50 Sex: 115 males 51 females Diagnosis: 100% opiate dependence Exclusions: - age range outside 18-50 years - not enrolled in a drug treatment programme - lack of sufficient social support (e.g. transportation, residence) - pregnancy - reactions to study medications or contraindications to detoxification - contraindications to naltrexone (e.g. severe chronic hepatitis or pain) - psychiatric conditions necessitating intensive services (e.g. suicidal depression) Baseline: GROUPS: Clonidine / clonidine + naltrexone / buprenorphine Age at first heroin use: 21.9 / 23.0 / 22.1 Years of heroin use: 8.9 / 7.7 / 8.5 Bags of heroin used in past 30 days: 3.8 / 4.0 / 3.3 Weekly cocaine use (g): 0.38 / 0.39 / 0.96 Withdrawal score: 15.7 / 17.3 / 15.3 Craving score: 72.9 / 79.4 / 77.6	**Data Used** Withdrawal severity Completion	**Group 1 N= 55** Alpha2 adrenergic agonist: clonidine - 0.1 0.2 mg every 4 hours as needed to control withdrawal symptoms on days 1-7 Opiate antagonist: naltrexone - Full blocking dose of 50 mg on day 8 Placebo - Placebos for buprenorphine **Group 2 N= 54** Alpha2 adrenergic agonist: clonidine - As per clonidine group Opiate antagonist: naltrexone - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Placebo - Placebos for buprenorphine **Group 3 N= 53** Opiate partial agonist: buprenorphine - 3 mg sublingual on days 1-3 Alpha2 adrenergic agonist: clonidine - As per clonidine group from day 4 Opiate antagonist: naltrexone - 25 mg on day 4, 50 mg on day 5	Study quality 1+
PETITJEAN2002				

Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 15 Setting: Inpatient unit, Switzerland Notes: RANDOMISATION: Method not reported	n= 37 Age: Mean 32 Sex: 28 males 9 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: Concurrent or benzodiazepine dependence -- these were treated prior to starting opiate detoxification Baseline: Not reported	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 19** Opiate partial agonist: buprenorphine with inpatient - Sublingual: 8 mg / 70 kg in 2 daily doses to max 16 mg / 70 kg reduced in 2 mg steps over average 12 days **Group 2 N= 18** Opiate agonist: methadone with inpatient - Oral: 40 mg / 70 kg in 2 daily doses to max 60 mg / 70kg reduced in 10 mg steps to 30 mg / 70 kg, then 5 mg steps over total of 15 days on average	Limited reporting in conference abstract; some additional data obtained from Cochrane review (unpublished data) Study quality: 1+
PONIZOVSKY2006 Study Type: RCT (randomised controlled trial) Study Description: Cluster randomised Blindness: Duration (days): Mean 10 Setting: Israel	n= 200 Age: Range 18-50 Sex: no information Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - <18 years or >50 years - comorbid serious physical illness - suicide risk - acute psychosis - severe depression - organic brain syndrome - dependence on benzodiazepines or alcohol - pregnancy or breastfeeding	**Data Used** Completion General Health Questionnaire (GHQ) Notes: DROPOUTS: Buprenorphine = 10/100, clonidine = 50/100	**Group 1 N= 100** Opiate partial agonist: buprenorphine with inpatient - Sublingually: 6 mg at 9 am and 4 mg at 4 pm on day 1; 4 mg at 9 am and 4 mg at 4 pm on days 2-3; 4 mg at 9 am and 2 mg at 4 pm on day 4; 4 mg on day 5; 2 mg on days 6-7; 1 mg on days 8-9. **Group 2 N= 100** Alpha2 adrenergic agonist: clonidine with inpatient - Tablets: 0.15 mg four times per day (every 4 hours) on days 1-4; 0.15 mg three times per day on days 5-8; 0.075 mg three times per day on days 9-10. Adjuvant therapy with promethazine, dipyrone, trazodone, phenobarbital, antiemetics	Study quality: 1+
RAISTRICK2005 Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 7 Followup: 1 month Setting: UK Info on Screening Process: 617 screened, 136 excluded (repeat detoxifications [n=95], florid psychosis [n=1], researcher unavailability [n=2], unstable substance use [n=19], dihydrocodeine [n=19])	n= 210 Age: Mean 28 Range 17-46 Sex: 157 males 53 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - repeat detoxifications - florid psychosis - unstable substance use - electing dihydrocodeine	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Abstinence: 1 month Completion Notes: DROPOUTS: Buprenorphine =37/107, lofexidine = 56/103	**Group 1 N= 107** Opiate partial agonist: buprenorphine with outpatient - 7-day taper: 4 mg day 1, 6-8 mg day 2, 6 mg day 3, 4 mg day 4, 2 mg day 5, 0.8 mg day 6, 0.4 mg day 7. Naltrexone offered 2 days after last dose **Group 2 N= 103** Alpha2 adrenergic agonist: lofexidine with outpatient - 0.4mg 4 hourly days 1- 4; in addition adjunctive medications of co-phenotype prn max 8 tablets (diarrhoea), hyoscine butylbromide prn max 80mg (ab cramps), chlordiazepoxide max 60mg (muscle aches), chlorpromazine 25-50mg (insomnia); then Naltrexone 25mg	271 refused to be randomised and chose between the two treatments Study quality 1+
SALEHI2006 Study Type: RCT (randomised controlled trial) Study Description: No evidence of allocation concealment Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 14 Followup: None Setting: University hospital in Iran; unclear whether detox actually took place within hospital Notes: Randomisation procedure not reported Info on Screening Process: 167 screened, 70	n= 70 Age: Mean 37 Sex: all males Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age outside range 20-60 - contraindications for methadone or tramadol - taking 'extra medications' - polysubstance dependence - any major psychiatric disorder (bipolar, psychosis or major depressive disorder) - having objective signs of withdrawal when administered	**Data Used** Completion Withdrawal: Short Opiate Withdrawal Scale	**Group 1 N= 36** Opiate agonist: methadone - 15 mg per day methadone at entry, reduced by 15% per day to reach 0 at day 7. Placebo thereafter. Symptomatic - 0.3 mg / day clonidine, 10-30 mg / day oxazepam	Study quality: 1+

eligible and randomised	methadone 15 mg for one day Notes: PRIMARY DIAGNOSIS: Daily opium use (equivalent to <=15 mg methadone) Baseline: Methadone / tramadol Years of opiate dependence: 12.86 / 12.85 Short Opiate Withrawal Scale (SOWS) score at entry: 11.97 / 10.28 Daily opium use: unknown		**Group 2 N= 34** Opiate agonist: tramadol - 450 mg per day (equivalent to 15 mg methadone) at entry, reduced by 15% per day to reach 0 at day 7. Placebo thereafter. Symptomatic - 0.3 mg per day clonidine, 10-30 mg per day oxazepam	
SAN1990 Study Type: RCT (randomised controlled trial) Study Description: Per protocol Type of Analysis: Per protocol (completed >=12 days of treatment) Blindness: Double blind Duration (days): Mean 12 Setting: Inpatient, Spain Info on Screening Process: 170 enrolled, 80 failed to complete >=12 days of treatment. Data presented for completers only	n= 90 Age: Mean 24 Range 18-36 Sex: 72 males 18 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - psychopathological antecedents before opiate addiction - signs of cardiovascular diseases - previous participation in clinical trial Baseline: GROUPS: Clonidine / methadone / guanfacine Years of opiate use: 5.4 / 5.5 / 4.6 Previously attempted treatment: 24/30, 20/30, 20/30	**Data Used** Withdrawal severity Completion Retention: duration in treatment	**Group 1 N= 30** Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 1.05 mg / day - Tapered over 11 days. Initial dose titrated on body weight and recent heroin use **Group 2 N= 30** Opiate agonist: methadone with inpatient. Mean dose 37.3 mg / day - Tapered over 11 days. Initial dose titrated on body weight and recent heroin use Benzodiazepines as adjuncts as needed **Group 3 N= 30** Alpha2 adrenergic agonist: guanfacine with inpatient. Mean dose 3.58 mg / day - Tapered over 11 days. Initial dose titrated on body weight and recent heroin use	Study quality 1+
SAN1994 Study Type: RCT (randomised controlled trial) Study Description: Allocation by pharmacy Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 18	n= 144 Age: Mean 27 Sex: 102 males 42 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - history of psychiatric disorders - liver dysfunction - cardiovascular diseases - other addiction - pregnancy Notes: PRIMARY DIAGNOSIS: Heroin dependence Baseline: HIV+: 52%	**Data Used** Withdrawal: OWS (Opiate Withdrawal Syndrome) Withdrawal: OWC (Opiate Withdrawal Checklist) Completion	**Group 1 N= 75** Opiate agonist: methadone - Initial dose based on body weight and heroin consumption, tapered over 8 days to 10% of initial dose. Benzodiazepines/hypnotics as adjuncts as appropriate **Group 2 N= 26** Alpha2 adrenergic agonist: guanfacine with inpatient. Mean dose 4 mg - Beginning on day 9 Opiate agonist: methadone with inpatient - Initial dose based on body weight and heroin consumption, tapered over 8 days to 50% of initial dose and discontinued on day 9 **Group 3 N= 43** Alpha2 adrenergic agonist: guanfacine. Mean dose 3 mg - Beginning from day 9 Opiate agonist: methadone with inpatient - Initial dose based on body weight and heroin consumption, tapered over 8 days to 50% of initial dose and discontinued on day 9	Study quality 1++
SCHNEIDER2000 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 21 Setting: Germany Notes: RANDOMISATION: Method not reported	n= 27 Age: Mean 31 Sex: 24 males 3 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - participated in a structured drug trial in last 6	**Data Used** Completion	**Group 1 N= 12** Benzodiazepine: oxazepam with inpatient - 900 mg per day for 7 days then tapered and ceased on day 15. Received 900 mg carbamazepine per day for 7 days then tapered and ceased on day 20	Study quality 1+

	months - schizophrenia - bipolar disorder - hepatic disorder - cardiovascular disorder - abnormal ECG - chronic obstructive pulmonary disorder - pregnant Baseline: GROUPS: Buprenorphine / oxazepam Duration opiate use: 11.9 (5.4) / 8.7 (5.8)		**Group 2 N= 15** Opiate partial agonist: buprenorphine with inpatient - 3 mg per day for 7 days then tapered and ceased on day 11. Received 900 mg carbamazepine for 7 days then tapered and ceased on day 20.	
SEIFERT2002 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: No mention Duration (days): Mean 14 Setting: Germany	n= 26 Age: Mean 32 Sex: 22 males 4 females Diagnosis: 100% opiate dependence by DSM-IV Baseline: GROUPS: Methadone / buprenorphine Years of opiate misuse: 8.6 (6.8) / 10.5 (7.5)	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 14** Opiate partial agonist: buprenorphine with inpatient - 4 mg per day for 3 days then tapered to cease on day 10. Received 900 mg carbamazepine per day for 6 days then tapered to cease on day 14 **Group 2 N= 12** Opiate agonist: methadone with inpatient - 20 mg on day 1 tapered to cease on day 10. Received 900 mg carbamazepine for 6 days then tapered to cease on day 14	Study quality 1+
SEOANE1997 Study Type: RCT (randomised controlled trial) Study Description: Envelope-concealed allocation Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 1 Followup: 1 month Setting: Spain Notes: RANDOMISATION: Computer-generated random number table Info on Screening Process: 359 screened, 47 met exclusion criteria and 312 gave consent. 12 dropped out or were excluded prior to treatment, so 300 randomised.	n= 300 Age: Mean 30 Sex: 210 males 90 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - heroin consumption <100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption > 100 g / day - probable or known pregnancy - acute infectious pathology - cachexia or terminal disease - probable or known allergy to study medications - bronchospasm that fails to respond to inhaled beta2 agonists - psychosis Baseline: (GROUPS: Light / heavy sedation) Daily heroin use (mg): 735.3 / 747.2 Route: Intravenous: 39% / 46%; nasal: 19% / 20%; smoked: 17% / 19%; two or more: 25% / 15% Previous detoxification attempts: 4.6 / 4.4	**Data Used** Abstinence: 1 month Completion Withdrawal: Wang Scale Notes: No treatment comparisons given for completion and 1-month abstinence	**Group 1 N= 150** Opiate antagonist: naloxone with inpatient - After sedation, 0.06-0.08 mg / kg intravenous infusion for 5-10 min Symptomatic with inpatient. Mean dose 0.7 mg / kg - Metoclopramide to increase gastric emptying after sedation has begun Anaesthetic: propofol with inpatient - Initiation with bolus at 0.3mg/kg combined with bolus of midazolam at 0.04mg/kg. Maintenance, for 6-8 hours, consisted of continuous infusion of propofol initially at 3mg/kg/hr, +/-10% previous dose as indicated, combined with midazolam at 0.10mg/kg/hr Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - Administered via nasal-gastric probe after naloxone. Maintenance oral dose (50 mg) dispensed after discharge for 1 year Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 3 mg / kg - Administered subcutaneously every four hours after sedation had begun	Study quality: 1++

			Group 2 N= 150 Opiate antagonist: naloxone with inpatien Symptomatic with inpatient Anaesthetic: propofol with inpatient - As per light sedation group, but bolus infusion lasted only the time necessary to put the patient to sleep (usually 2-4min); maintenance sedation was started immediately thereafter Opiate antagonist: naltrexone with inpatient Alpha2 adrenergic agonist: clonidine with inpatient	
SHEARD2007 Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 16 Followup: 6 months Setting: Prison in UK Notes: RANDOMISATION: computer randomised CONCEALMENT OF ALLOCATION: opaque sealed envelopes	n= 90 Age: Range 16-65 Sex: no information Diagnosis: 100% opiate misuse Exclusions: - <18 years >65 years - negative urine for illicit opiates - remaining in custody for <28 days - contraindications for buprenorphine or methadone - co-existing acute medical conditions requiring emergency admission - currently undergoing detox from other addictive drugs	**Data Used** Abstinence: 3 months Abstinence: endpoint	**Group 1 N= 42** Opiate partial agonist: buprenorphine with prison - reducing regimen of buprenorphine over a period less than 16 days at the discretion of the prescribing doctor **Group 2 N= 48** Opiate agonist: dihydrocodeine with prison - reducing regimen of dihydrocodeine over a period less than 16 days at the discretion of the prescribing doctor	Study quality 1+
SORENSEN1982 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatient detoxification clinic, San Francisco, US Notes: RANDOMISATION: Stratified by employment status	n= 61 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by urinalysis Exclusions: - age < 18 - no evidence of physical addiction to opiates - life-threatening medical conditions Notes: PRIMARY DIAGNOSIS: Heroin dependence ETHNICITY: 53% White, 36% Hispanic, 11% Other Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment	**Data Used** Entry to further treatment: MMT Entry to further treatment Completion Abstinence: endpoint **Data Not Used** Abstinence: 3 months	**Group 1 N= 18** Opiate agonist: methadone with outpatient - 6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral **Group 2 N= 15** Opiate agonist: LAAM with outpatient - 6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral **Group 3 N= 13** Opiate agonist: LAAM - 3-week detox: 30mg on day 1; optional 10mg methadone on day 2 if showing withdrawal symptoms, 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling and referral	Study quality 1+

			Group 4 N= 15 Opiate agonist: methadone with outpatient - 3-week detox: 30mg on day 1; raised to 40mg on day 2 if showing withdrawal symptoms; 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling, and referra	
TENNANT1975 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 21 Followup: 1 month Setting: Los Angeles, USA Notes: RANDOMISATION: No details	n= 72 Age: Mean 28 Sex: 57 males 15 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: Age <18 Notes: PRIMARY DIAGNOSIS: By history, needle marks, positive urine test and observation of withdrawal symptoms ETHNICITY: 53% White Baseline: GROUPS: Methadone / propoxyphene napsylate Years of heroin use: 7.8 / 9.1 Months of daily heroin use: 8.8 / 7.0	**Data Used** Entry to further treatment: MMT Opiate use Abstinence: 1 month Completion	**Group 1 N= 36** Opiate agonist: propoxyphene napsylate with outpatient - Initial dose 800 mg, tapered daily **Group 2 N= 36** Opiate agonist: methadone with outpatient - Initial dose 24 mg, tapered daily	Study quality 1+
TENNANT1978 Study Type: RCT (randomised controlled trial) Study Description: Double dummy - all participants received the same number of capsules Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 42 Followup: 6 months Setting: California, USA Notes: Randomisation procedures not reported Info on Screening Process: 70 screened, 22 eligible and randomised	n= 22 Age: Mean 37 Sex: 15 males 7 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT Exclusions: - not on MMT for >=3 months, or not wishing to withdraw - not declared 'above average' in psychosocial rehabilitation as judged by the referring MMT programme - evidence of heroin or other drug misuse in past 30 days - not stabilised on 30 mg methadone for at least 10 days - any medical or psychiatric illness requiring psychoactive drug therapy Notes: ETHNICITY: 82% White Baseline: GROUPS: methadone / propoxyphene Years of heroin use: 16.0 / 13.6 Months of methadone use: 33.2 / 33.8 Highest methadone dose (mg): 78.3 / 86.0	**Data Used** Withdrawal severity Opiate use Retention: duration in treatment Completion Notes: 1-month and 6-month follow-ups	**Group 1 N= 12** Placebo - Placebo capsules Opiate agonist: methadone with outpatient. Mean dose tablet form - Starting dose 30 mg (15 mg in-clinic, 15 mg take-home) reduced by 5 mg every 5 days, down to 2.5 mg by day 35 through to day 42; tapered to 0 on day 43. **Group 2 N= 10** Opiate agonist: propoxyphene napsylate with outpatient - 100 mg in-clinic and 300 mg take-home dose from day 5; raised to 1100 mg total (600 mg in-clinic plus 500 mg take-home) by day 25; tapered to 0 by day 43. Placebo - Placebo capsules Opiate agonist: methadone - Administered in clinic. Starting dose 30 mg, reduced by 5 mg every 5 days down to 0 mg by day 25.	Study quality 1+
UMBRICHT1999 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Range 4-8 Setting: Residential research ward, Baltimore, USA Notes: Randomisation procedure not described Info on Screening Process: 33 ineligible; 47 didn't complete screening evaluation so 60	n= 60 Age: Mean 31 Sex: 29 males 31 females Diagnosis: opiate dependence by DSM-IV Exclusions: - not aged 18-40 - prior seizure disorders - cardiac ischaemia - hypertension	**Data Used** Completion Withdrawal: OOWS (Objective Opiate Withdrawal)	**Group 1 N= 32** Opiate antagonist: naltrexone - 0 mg day 1, 12 mg days 2-3, 25 mg day 4, 50 mg thereafter Symptomatic - Clonidine and other medications prescribed according to standard indications for opiate withdrawal when OOWS score >=5	Study quality: 1+

randomised.	- diabetes mellitus - AIDS (CD4 T-cell count <200 / ml) - psychosis or suicidal ideation - current asthma - liver transaminases - acute need for medical care - pregnancy or lactation Baseline: Placebo / naltrexone Years of heroin use: 6.5 / 8.3 Days of heroin use in past 30: 29 / 29 Years of cocaine use: 3.6 / 4.7 Days of cocaine use (past 30): 12 / 10 $ on drugs past 30 days: 1180 / 930 Injection drug use: 29% / 31% Previous treatment attempts: 1.0 / 0.8	Notes: Use of adjuncts and reasons for leaving study were reported; no follow-up outcomes DROPOUTS: 24% placebo, 44% naltrexone	Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8 **Group 2 N= 28** Opiate antagonist: naltrexone - Placebo days 1-7, naltrexone 50 mg (maintenance dose) on day 8. Placebo contained 50 mg acetaminophen to mimic bitterness of naltrexone. Symptomatic - Clonidine and other medications prescribed according to standard indications for opiate withdrawal when OOWS score >=5 Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8	
UMBRICHT2003 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design (all participants received oral and sublingual doses daily) Blindness: Double blind Duration (days): Mean 56 Setting: AIDS service US Notes: RANDOMISATION: Method not reported Info on Screening Process: 63 enrolled, 8 excluded from analysis (3 dropped out prior to receiving any study medication, 5 due to medication errors)	n= 55 Age: Mean 40 Sex: 30 males 25 females Diagnosis: 100% opiate dependence by urinalysis 100% HIV positive Exclusions: - not HIV seropositive - age <18 - no hospitalisation for an acute medical illness - alcohol dependence - acute psychosis or AIDS dementia - hypotension, bradycardia or coagulopathy - thrombocytopenia precluding intramuscular injections - undergoing MMT Notes: 95-100% African American Baseline: Years of drug use = 18	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 18** Opiate agonist: methadone with inpatient - 3-day taper: 30 mg day 1, 20 mg day 2, 10 mg day 3 **Group 2 N= 21** Opiate partial agonist: buprenorphine with inpatient - 3-day taper: 0.6 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3. **Group 3 N= 16** Alpha2 adrenergic agonist: clonidine with inpatient - 3-day taper: 0.2 mg loading dose and 0.1 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3	6-month study consisted of 4-month induction/maintenance phase followed by 2-month detoxification phase Study quality 1+
WASHTON1980 Study Type: RCT (randomised controlled trial) Study Description: Double-dummy design Blindness: Double blind Duration (days): Mean 10 Setting: USA Notes: RANDOMISATION: Method not reported	n= 26 Age: Mean 31 Sex: 22 males 4 females Diagnosis: 100% opiate dependence Exclusions: Evidence of serious medical or psychiatric illness Baseline: Mean years of heroin use: 10	**Data Used** Completion	**Group 1 N= 13** Opiate agonist: methadone - 15-30 mg starting maintenance dose, reduced by 1 mg / day until 0 reached **Group 2 N= 13** Alpha2 adrenergic agonist: clonidine - Abrupt substitution of clonidine for methadone	Study quality: 1+
WRIGHT2007A Study Type: RCT (randomised controlled trial) Study Description: Allocation centrally performed and concealed in opaque sealed envelopes Type of Analysis: ITT	n= 60 Age: Mean 29 Sex: 42 males 18 females Diagnosis: 100% opiate misuse by urinalysis Exclusions: - age <18	**Data Used** Mortality Abstinence: 3 months Abstinence: endpoint Completion	**Group 1 N= 28** Opiate partial agonist: buprenorphine with outpatient. Mean dose max 8 mg - Dispensed as either 8 mg, 2 mg or 0.4 mg sublingual tablet under daily supervision. Within standard regimen (max 8 mg/day, on days 2-3), but at discretion of prescribing doctors, who	Study quality +1

Blindness: Open Duration (days): Mean 15 Setting: 10 general practices in Leeds, UK Notes: Randomisation by random block size, stratified by practice and concealed in sealed opaque envelopes. Used Excel RAND function. Info on Screening Process: 60 randomised	- not using street opiates as confirmed by urinalysis - contraindications to study medications - had been randomised into trial previously Notes: PRIMARY DIAGNOSIS: Using street opiates - 63% intravenous, 35% smoked, 2% both Baseline: (Buprenorphine / dihydrocodeine) Years of opiate use: 8.8 (4.9) / 7.0 (3.7) Daily opiate use £: min 17.1 (8.1) / 15.6 (7.2), max 23.2 (12.1) / 18.1 (9.0) Illicit opiates in initial urine: 82% / 84% Other drugs in initial urine: 64% / 37% 'Severely dependent': 28% / 31%		were free to titrate dose against symptoms. **Group 2 N= 32** Opiate agonist: dihydrocodeine with outpatient - Dispensed as 30 mg rapid-release tablets in take-home instalments; each instalment for min 3 and max 4 daily doses	

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
AHMADI2004A	Maintenance study
AMASS1994	n <10 per group
AMASS2004	Only data for treatment group provided
BEARN1998	Assignment not random - patient preference
BICKEL1988	Not required outcomes
CAMI1985	Does not adequately address question
CAMI1992	Not assessing efficacy of detoxification treatments
DAWE1995	Small sample size
FINGERHOOD2001	Not RCT
HAMEEDI1997	n<20
HARTMANN1991	n<20
KOSTEN1984	No extractable outcomes
KOSTEN1985	No extractable data
KOSTEN1992A	No treatment comparison for withdrawal phase
KOURI1996	No relevant outcomes; n<10 per group
KRABBE2003	Not randomised
ORESKOVICH2005	n<10 per group
PINI1991	Small sample size
SEES2000A	Compares detoxification with maintenance - not relevant
SIGMON2004	n<10 per group
WILSON1993	Not an RCT

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Characteristics of reviewed studies: Dosage of opioid detoxification

Comparisons Included in this Clinical Question

Exponential Versus Linear Dose Reduction	Full Information Versus Standard Information	High Versus Moderate Starting Dose	Variable Versus Fixed Dosage
STRANG1990	GREEN1988	BANYS1994 STRAIN1999	DAWE1991

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BANYS1994 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 180 Setting: San Francisco, US	n= 38 Age: Range 18-65 Sex: 22 males 16 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - age outside range 18-65 - no accessible veins - pregnant - contraindications to high-dose methadone - been on methadone in past 30 days - negative opiate or positive methadone urine screen - <3 objective signs of opiate withdrawal Baseline: Positive urinalysis for other drugs: 38% cocaine, 8% amphetamine, 11% benzodiazepine, 3% barbiturates	**Data Used** Urinalysis Withdrawal severity Retention: duration in treatment Notes: Twice weekly urine screens on random days; either test being positive marked as positive for that week	**Group 1 N= 19** Opiate agonist: methadone with outpatient - High-dose group: started on 30 mg, raised to 80 mg over 10 days, maintained until day 101, then tapered linearly during days 102-180 **Group 2 N= 19** Opiate agonist: methadone with outpatient - Low-dose group: started on 30 mg, raised to 40 mg on day 2, maintained until day 101, then tapered linearly to 0 over days 102-180 (with 1 mg on days 178-180)	Two patients from high-dose group could not tolerate full 80 mg dose and were analysed in low-dose group, and excluded from analysis subsequently Study quality 1+
DAWE1991 Study Type: RCT (randomised controlled trial) Study Description: Participants not told that they were being randomised to two withdrawal schedules Blindness: Single blind Duration (days): Mean 70 Setting: Outpatient detox in south London Info on Screening Process: 82 eligible and randomised > 39 attended first session	n= 39 Age: Mean 26 Sex: 28 males 11 females Diagnosis: 100% opiate dependence by urinalysis Exclusions: - Pregnant - Considered inappropriate on clinical grounds Baseline: Mean years of opiate use: 7 Mean age at first use: 19 Administration: 38% IV, 53% inhaled, 9% IV and inhaled Sharing injecting equipment: 56% ever, 29% in past year	**Data Used** Retention: duration in treatment Completion	**Group 1 N= 24** Opiate agonist: methadone with outpatient - Flexible dosage: Initial dose established as per fixed group, but thereafter participants could negotiate dose levels and rate of reduction. It was made clear that their aim was to reduce their dose to 0 within about 6 weeks. Otherwise as per fixed group **Group 2 N= 15** Opiate agonist: methadone with outpatient - Fixed dosage: Initial dose set according to DHSS guidelines, tapered over 6 weeks at a constant rate. Patient seen at least once a week by doctor and keyworker, and required to attend weekly support group and individual session	Study quality 1+
GREEN1988 Study Type: RCT (randomised controlled trial) Study Description: No mention Blindness: Single blind Duration (days): Mean 21 Setting: Bethlem Royal Hospital, London Info on Screening Process: 35 admitted for detoxification - five excluded (three left study before start of detox, two failed to comply with form-filling) > 30 randomised	n= 30 Age: Mean 25 Range 19-35 Sex: 23 males 7 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: Not reported Notes: PRIMARY DIAGNOSIS: 33/35 heroin, 2/35 prescribed methadone Baseline: Mean years of opiate dependence: 6	**Data Used** Completion Withdrawal: OWS (Opiate Withdrawal Syndrome)	**Group 1 N= 15** Opiate agonist: methadone with inpatient - 3 times daily oral methadone, linear reduction schedule. Given detailed withdrawal information which was not part of routine treatment, e.g. regarding length/intensity of symptoms they might experience; specific concerns or anxiety discussed and addressed	Study Quality 1+

			Group 2 N= 15 Opiate agonist: methadone with inpatient - 3 times daily oral methadone, linear reduction schedule. Given standard information about admission and ward routine, and usual responses to any requests for information or reassurance.	
STRAIN1999 Study Type: RCT (randomised controlled trial) Study Description: Randomisation in sealed envelopes by pharmacy staff and RAs without any patient contact. Dosage always double-blinded; methadone administered in syrup Blindness: Double blind Duration (days): Mean 280 Setting: 40-week outpatient methadone programme, US Notes: RANDOMISATION: Stratified on cocaine-use status and level of opiate use Info on Screening Process: 192 randomised; 111 completed stabilisation phase and entered taper phase	n= 192 Age: Mean 38 Sex: 124 males 68 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - age < 18 - no documentation of >=2 previous methadone detoxification attempts, no opiate-positive urine sample or no physical evidence for needle use - any chronic medical illness - any major mental illness - positive pregnancy test result - treatment at this clinic in past month Notes: ETHNICITY: 94% White Baseline: GROUPS: Moderate dose / high dose Legally free: 66.0% / 77.9% Previous treatments: 4.0 / 4.2 Use in past week: opiates 25.8 / 24.7; cocaine 4.5 / 6.6; benzodiazepines 0.2 / 0.2	**Data Used** Completion Opiate use Urinalysis	**Group 1 N= 97** Opiate agonist: methadone with outpatient - Wk1: 30mg; Wks2-6: 2mg increase each week (up to 40mg/day) Wks8-30: If 2 of past 4 urines tested opiate +ve, 5mg dose increase given (up to max 50mg); dose decreased at patient's request, or if past 6 urines -ve Wks31-40: Tapered at rate of 10% per week Psychosocial: group therapy - Counsellor set treatment goals and developed individual treatment plan. Weekly individual and group therapy focusing on relapse prevention **Group 2 N= 95** Psychosocial: group therapy - As per moderate-dose group Opiate agonist: methadone - Wk 1: 30mg Wks 2-6: 2mg increase each wk (up to 80mg/day) Wks8-30: If 2 of past 4 urines tested opiate +ve, 10mg dose increase given (up to max 100mg); dose decreased at patient's request, or if past 6 urines -ve Wks31-40: Tapered at rate of 10% per wk	Study quality 1++
STRANG1990 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 10 Followup: 15 days Setting: Inpatient DDU, London	n= 87 Age: Mean 28 Sex: 64 males 23 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - Detoxification not required, or longer detoxification required (e.g. pregnancy) Notes: PRIMARY DIAGNOSIS: Heroin or methadone addicts Baseline: Almost all subjects used other drugs	**Data Used** Retention: duration in treatment Withdrawal: OWS (Opiate Withdrawal Syndrome) Completion	**Group 1 N= 43** Opiate agonist: methadone with inpatient - Linear: Dose initially titrated against withdrawal symptoms, reduced per day by 10% of starting dose. All doses delivered three times daily in 20ml fluid. No other drugs apart from tapered diazepam for BDZ codependence **Group 2 N= 44** Opiate agonist: methadone with inpatient - Exponential: Dose initially titrated against withdrawal symptoms, reduced each day by 20% of yesterday's dose. All doses delivered three times daily in 20ml fluid. No other drugs apart from tapered diazepam for BDZ codependence	Study Quality 1+

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Characteristics of reviewed studies: Duration of opioid detoxification

Comparisons Included in this Clinical Question

1 Week Versus 3 Weeks
SENAY1981
SORENSEN1982
STITZER1984

Ultrarapid (<=24 Hours) Versus Rapid (1-7 Days)
ASSADI2004
COLLINS2005
DEJONG2005
FAVRAT2006
SEOANE1997

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ASSADI2004 Study Type: RCT (randomised controlled trial) Type of Analysis: LOCF Blindness: Double blind Duration (days): Mean 5 Setting: Iran Notes: RANDOMISATION: computer generated list of random numbers	n= 40 Age: Mean 32 Sex: 39 males 1 female Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - <18 years >60 years - pregnancy or lactation - clinically unstable medical illness - liver transaminases exceeding twice upper limit of normal - history of psychosis - mania or severe depression - concurrent dependency on alcohol - antisocial or borderline personality disorder Baseline: Mean duration of opioid use = 9 years	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 20** Opiate partial agonist: buprenorphine with inpatient - 5 day taper: 2 x 1.5mg day 1, tapered to 2 x 0.3mg day 5. Indomethacin, trazadone, chlorpromazine, hyoscine adjunct medications as required. Relapse prevention using naltrexone **Group 2 N= 20** Opiate partial agonist: buprenorphine with inpatient - 24 hour taper: 4 x 1.5mg between 12pm and 6pm day 1, 4 x 1.5mg between 6am and 12pm day 2. Received indomethacin, trazadone, chlorpromazine, hyoscine, adjunct medications as required. Relapse prevention using naltrexone. Placebo saline remainder of study	Study quality 1++
COLLINS2005 Study Type: RCT (randomised controlled trial) Study Description: Patients not blinded Type of Analysis: ITT Blindness: Single blind Duration (days): Mean 84 Setting: US 3 days' inpatient phase followed by 12 weeks' outpatient phase Notes: RANDOMISATION: Blocks of 12 with computer-generated assignments ALLOCATION: Staff remained unaware of randomisation sequence Info on Screening Process: 169 screened; 35 met exclusion criteria and 28 lost to follow-up or refused consent; 106 enrolled and randomised	n= 106 Age: Mean 36 Range 21-50 Sex: 76 males 30 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age outside 21-50 range - poor general health or acute medical illness - DSM-IV criteria for dependence on alcohol or non-opiate drugs - pregnancy or lactation or failure to use adequate birth control - history of significant violent behaviour - schizophrenia and/or major mood disorder - suicide risk - current psychotropic medication, MAO inhibitors, protease inhibitors - positive cocaine urinalysis on admission - BMI > 40 - Blood glucose concentration > 160 mg/L - history of food or drug allergy, sensitivity to study medication Notes: PRIMARY DIAGNOSIS: Opiate dependence >=6 months and seeking treatment ETHNICITY: 53% White	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Completion Retention: duration in treatment	**Group 1 N= 37** Opiate partial agonist: buprenorphine with inpatient. Mean dose 8 mg - Single sublingual dose on evening of day 1 Symptomatic with inpatient - As needed Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Opiate antagonist: naltrexone with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days Alpha2 adrenergic agonist: clonidine with inpatient - As needed	Study quality: 1++

	Baseline: (GROUPS: ultrarapid / buprenorphine / clonidine) Heroin use (days in past 30): 30 / 29 / 29 Lifetime heroin use disorder (years): 7.6 / 7.4 / 6.4 Previous inpatient detoxification attempts: 1.74 / 1.59 / 1.21 Previous inpatient rehabilitation attempts: 0.57 / 0.54 / 0.56 Previous outpatient detoxification attempts: 0.17 / 0.11 / 0.29 Previous MMT: 0.66 / 0.57 / 0.53		**Group 2 N= 34** Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Opiate antagonist: naltrexone with outpatient - Initial 12.5 mg dose on day 6, followed by 25 mg next day and 50 mg maintenance dose on subsequent days Alpha2 adrenergic agonist: clonidine with inpatient - As needed **Group 3 N= 35** Symptomatic with inpatient - As required: clonazepam, up to 2 mg every 8 hours; ketorolac, 30 mg intramuscularly every 6 hours; ondansetron, 8 mg orally every 8 hours or prochlorperazine, 10 mg orally/intramuscularly every 8 hours; octreotide, 100 mcg every 8 hours; and so on Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy Anaesthetic: propofol with inpatient - 25-150 mcg/kg per min; anaesthesia maintained for 2-4 hours Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - Induced on 50 mg then maintained throughout outpatient phase Alpha2 adrenergic agonist: clonidine with inpatient - As needed, up to 0.2 mg every 4 hours (max 1.2 mg/day)	
DEJONG2005 Study Type: RCT (randomised controlled trial) Study Description: 7 days' inpatient treatment followed by 10 months' outpatient community reinforcement approach Type of Analysis: ITT Blindness: Open Duration (days): Mean 300 Setting: Four addiction treatment centres in the Netherlands Notes: RANDOMISATION: Centralised and computerised, in blocks of two Info on Screening Process: 296 screened, 24 met exclusion criteria or refused consent; 272 enrolled and randomised	n= 272 Age: Mean 36 Sex: 223 males 49 females Diagnosis: opiate dependence by DSM-IV Exclusions: - age <18 - no previous unsuccessful detox attempts - lack of a non-opiate user in social network - severe somatic or psychiatric disorders - pregnancy - AIDS - contraindications to general anaesthesia - cocaine use in past 48 hours Baseline: (GROUPS: ultrarapid / no anaesthesia) Years of heroin use: 12.0 / 12.1 Age first heroin use: 20.9 / 20.8	**Data Used** Withdrawal: Subjective Opiate Withdrawal Scale Urinalysis Opiate use Withdrawal: COWS (Clinical Opiate Withdrawal) Abstinence: 1 month	**Group 1 N= 137** Symptomatic with inpatient - As per ultrarapid group Psychosocial: CRA (community reinforcement apprch) with outpatient - As per ultrarapid group Opiate antagonist: naltrexone with inpatient - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Alpha2 adrenergic agonist: clonidine with inpatient - As per ultrarapid group	Study quality: 1++

	Previous detoxification attempts: 7.4 / 8.4 Heroin use past 30 days: 18.0 / 18.8 Methadone use past 30 days: 22.0 / 23.6		**Group 2 N= 135** Symptomatic with inpatient - All participants treated with same medications at same dosages: 8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotride, ondansetron, butylscopolamine, diazepam; haloperidol and midazolam as necessary Anaesthetic: propofol with inpatient. Mean dose 5000 ng/ml - Anaesthesia induced on first signs of opiate withdrawal, using target controlled infusion method, and maintained for 4 hours Psychosocial: CRA (community reinforcement apprch) with outpatient - 23 sessions over 10 months: 10 monitoring naltrexone compliance, addictive behaviours and craving; 13 working on drug-refusal behaviour, relational issues, problem solving, social skills training and craving management with accompanying non drug user Opiate antagonist: naltrexone with inpatient - Administered at 9 am to precipitate withdrawal. At the end of anaesthesia, 100 mg administered through orogastric tube. Continued on maintenance dose (50 mg) for 10 months Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.3 mg - Administered at 9 am to prevent high blood pressure Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day	
FAVRAT2006 Study Type: RCT (randomised controlled trial) Study Description: Randomisation by pharmacist Type of Analysis: ITT Blindness: No mention Duration (days): Range 1-7 Setting: Switzerland Notes: RANDOMISATION: Computer-generated numbers Info on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised	n= 70 Age: Mean 30 Sex: 54 males 16 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age <18 - alcohol, cocaine or benzodiazepine dependence, or positive urinalysis prior to starting treatment - pregnancy - known idiosyncratic reactions - severe psychiatric comorbidity - other serious medical conditions Baseline: (Ultra-rapid / clonidine) ASI (drug): 0.34 / 0.35	**Data Used** ASI (Addiction Severity Index) Completion Abstinence: 12 months Abstinence: 3 months Notes: Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine FOLLOW-UPS: At 3, 6 and 12 months	**Group 1 N= 34** Psychosocial: individual therapy with outpatient - As per ultrarapid group Symptomatic with inpatient - Limited to one drug at one dosage per indication: loperamide 4 mg, tolperisone 150 mg, ondansetron 4 mg, zolpidem 10 mg, olanzapine 5 mg, paracetamol 500 mg Alpha2 adrenergic agonist: clonidine with inpatient - 0.600 mg/day for first 3 days, 0.300 mg on day 4, 0.225 mg on day 5, 0.150 mg on day 6 and 0.075 mg on day 7 (in divided 0.075 mg doses)	Study quality: 1++

			Group 2 N= 36 Psychosocial: individual therapy with outpatient - One week of "intensive" psychosocial support following discharge Symptomatic with inpatient - During anaesthesia, octreotide. After anaesthesia, during recovery phase: 30 mg intravenous ketorolac, glycopyrrolate if needed and 5 mg droperidol for delirium if needed. Anaesthetic: propofol with inpatient - Monitored and maintained at bispectral index 45-60 by propofol infusion (around 5-6 hours) Opiate antagonist: naltrexone with inpatient. Mean dose 100 mg - Oral, with 30 mg oral sodium citrate to precipitate withdrawal. Before leaving ICU, 24 hours after start of treatment, initiation of maintenance dose (50 mg) oral naltrexon Alpha2 adrenergic agonist: clonidine with inpatient - During anaesthesia, clonidine or lidocaine used to deepen anaesthesia and control withdrawal signs	
SENAY1981 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 90 Setting: Chicago, US	n= 72 Age: Mean 25 Sex: 40 males 32 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - Age <18 - Poor general health - Eligibility for MMT (with >2 years addiction history) - <6 months IV heroin use, or no period of daily use >=3 months - No objective clinical evidence of IV use (e.g. needle marks) - No history of withdrawal symptoms Notes: ETHNICITY: 53% Black, 14% White, 7% Other Baseline: (GROUPS: 3-week / 12-week) Mean starting methadone dose: 20.6mg Polydrug use: 82% / 81% Mean time to first treatment episode: 23 months Mean length of past 'run' of drug use: 11.6 months	**Data Used** Withdrawal severity Completion Abstinence: endpoint Retention: duration in treatment	**Group 1 N= 35** Psychosocial: group therapy - Intensive individual and group counselling Opiate agonist: methadone with outpatient - 3-week detox: Decreasing doses of methadone according to predetermined schedule for 21 days (with larger decrements at the beginning), followed by placebo for 69 days. Dose adjustment allowed during 1st week if experienced moderate or marked discomfort **Group 2 N= 37** Psychosocial: group therapy - Intensive individual and group counselling Opiate agonist: methadone with outpatient - 12-week detox: Methadone taper for 84 days and placebo for final week. Dose adjustment allowed during 1st week if patient experienced moderate or marked discomfort	Study quality 1+
SEOANE1997 Study Type: RCT (randomised controlled trial) Study Description: Envelope-concealed allocation Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 1 Followup: 1 month Setting: Spain Notes: RANDOMISATION: Computer-generated random number table Info on Screening Process: 359 screened, 47	n= 300 Age: Mean 30 Sex: 210 males 90 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - heroin consumption <100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption > 100 g / day - probable or known pregnancy - acute infectious pathology - cachexia or terminal disease	**Data Used** Abstinence: 1 month Completion Withdrawal: Wang Scale Notes: No treatment comparisons given for completion and 1-month abstinence	**Group 1 N= 150** Opiate antagonist: naloxone with inpatient - After sedation, 0.06-0.08 mg / kg intravenous infusion for 5-10 min Symptomatic with inpatient. Mean dose 0.7 mg / kg - Metoclopramide to increase gastric emptying after sedation has begur	Study quality: 1++

met exclusion criteria and 312 gave consent. 12 dropped out or were excluded prior to treatment, so 300 randomised.	- probable or known allergy to study medications - bronchospasm that fails to respond to inhaled beta2 agonists - psychosis Baseline: (GROUPS: Light / heavy sedation) Daily heroin use (mg): 735.3 / 747.2 Route: Intravenous: 39% / 46%; nasal: 19% / 20%; smoked: 17% / 19%; two or more: 25% / 15% Previous detoxification attempts: 4.6 / 4.4		Anaesthetic: propofol with inpatient - Initiation with bolus at 0.3mg/kg combinec with bolus of midazolam at 0.04mg/kg. Maintenance, for 6-8 hours, consisted of continuous infusion of propofol initially at 3mg/kg/hr, +/-10% previous dose as indicated, combined with midazolam at 0.10mg/kg/hr Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - Administered via nasal-gastric probe after naloxone. Maintenance oral dose (50 mg) dispensed after discharge for 1 year Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 3 mg / kg - Administered subcutaneously every four hours after sedation had begun **Group 2 N= 150** Opiate antagonist: naloxone with inpatien Symptomatic with inpatient Anaesthetic: propofol with inpatient - As per light sedation group, but bolus infusion lasted only the time necessary to put the patient to sleep (usually 2-4min); maintenance sedation was started immediately thereafter Opiate antagonist: naltrexone with inpatient Alpha2 adrenergic agonist: clonidine with inpatient	
SORENSEN1982 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatient detoxification clinic, San Francisco, US Notes: RANDOMISATION: Stratified by employment status	n= 61 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by urinalysis Exclusions: - age < 18 - no evidence of physical addiction to opiates - life-threatening medical conditions Notes: PRIMARY DIAGNOSIS: Heroin dependence ETHNICITY: 53% White, 36% Hispanic, 11% Other Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment	**Data Used** Entry to further treatment: MMT Entry to further treatment Completion Abstinence: endpoint **Data Not Used** Abstinence: 3 months	**Group 1 N= 18** Opiate agonist: methadone with outpatient - 6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral **Group 2 N= 15** Opiate agonist: LAAM with outpatient - 6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral **Group 3 N= 13** Opiate agonist: LAAM - 3-week detox: 30mg on day 1; optional 10mg methadone on day 2 if showing withdrawal symptoms, 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling and referral **Group 4 N= 15** Opiate agonist: methadone with outpatient - 3-week detox: 30mg on day 1; raised to 40mg on day 2 if showing withdrawal symptoms; 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling, and referra	Study quality 1+

STITZER1984 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 70 Setting: Outpatient research unit, Baltimore, US Info on Screening Process: 104 admitted to outpatient detox > 26 had >=50% +ve urinalysis during 3 week enrolment phase and randomised	n= 26 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence Baseline: Mean length of opiate addiction: about 8 years Previous MMT or methadone detox involvement: about half	**Data Used** Urinalysis Retention: duration in treatment	**Group 1 N= 13** Opiate agonist: methadone with outpatient. Mean dose 60mg - Dose raised from initial 30mg to 60mg over weeks 1-2, then lowered by 10mg steps at start of weeks 3, 5, 7, 8, 9, 10. Methadone delivered daily in cherry syrup supervised by nurse **Group 2 N= 13** Opiate agonist: methadone with outpatient. Mean dose 30mg - Dose maintained at 30mg through to end of week 7, then reduced in 10mg at start of weeks 8, 9 and 10. Methadone delivered in cherry syrup supervised by nurse	All participants stabilised on 30 or 40mg methadone during 3-week induction phase Study quality 1+

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
GOUREVITCH1999	Not detox

References of Included Studies

ASSADI2004 (Published Data Only)

Assadi, S. M., Hafezi, M., Mokri, A., et al. (2004) Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. Journal of Substance Abuse Treatment, 27, 75-82.

COLLINS2005 (Published Data Only)

Collins, E.D., Kleber, H.D., Whittington, R.A., et al. (2005) Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. The Journal of the American Medical Association, 294, 903-913.

DEJONG2005 (Published Data Only)

De Jong, C.A., Laheij, R.J. & Krabbe, P.F. (2005) General anaesthesia does not improve outcome in opioid antagonist detoxification treatment: a randomized controlled trial. Addiction, 100, 206-215.

FAVRAT2006 (Published Data Only)

Favrat, B., Zimmermann, G., Zullino, D., et al. (2006) Opioid antagonist detoxification under anaesthesia versus traditional clonidine detoxification combined with an additional week of psychosocial support: a randomised clinical trial. Drug and Alcohol Dependence, 81, 109-116.

SENAY1981 (Published Data Only)

Senay, E. C., Dorus, W. & Showalter, C. V. (1981) Short-term detoxification with methadone. Annals of the New York Academy of Sciences, 362, 203-216.

SEOANE1997 (Published Data Only)

Seoane, A., Carrasco, G., Cabre, L., et al. (1997) Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. British Journal of Psychiatry, 171, 340-345.

SORENSEN1982 (Published Data Only)

Sorensen, J.L., Hargreaves, W.A. & Weinberg, J.A. (1982) Withdrawal from heroin in three or six weeks. Comparison of methadyl acetate and methadone. Archives of General Psychiatry, 39, 167-171.

STITZER1984 (Published Data Only)

Stitzer, M. L., McCaul, M. E., Bigelow, G. E., & Liebson, I. A. (1984). Chronic opiate use during methadone detoxification: effects of a dose increase treatment. Drug & Alcohol Dependence, 14, 37-44.

References of Excluded Studies

GOUREVITCH1999 (Published Data Only)

Gourevitch, M. N., Hartel, D., Tenore, P., et al. (1999) Three oral formulations of methadone. A clinical and pharmacodynamic comparison. Journal of Substance Abuse Treatment, 17, 237-241.

Characteristics of reviewed studies: Efficacy of physical interventions

Comparisons Included in this Clinical Question

(Methadone + Acupuncture) Versus Methadone
ZENG2005

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ZENG2005 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 10 Setting: China, Drug Rehabilitation Centre Notes: RANDOMISATION: no mention of method used	n= 70 Age: Mean 34 Sex: 60 males 10 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - <18 >50 years of age - physical and psychiatric problems Baseline: Methadone + acupuncture/methadone Years of opiate use: 6.00(2.82)/6.23(2.93)	**Data Used** Withdrawal severity Completion Notes: DROPOUTS: Methadone + acupuncture 4/35 methadone = 9/35	**Group 1 N= 35** Opiate agonist: methadone with inpatient - Received methadone once a day. Starting dose 1mg/kg then reduced daily by approx 20% until 1 mg on day 10 and zero dose on day 11 Acupuncture with inpatient - Received acupuncture once a day. Needles were retained for 30 minutes, during which they were manipulated three times **Group 2 N= 35** Opiate agonist: methadone with inpatient - Received methadone once a day. Starting dose 1mg/kg then reduced daily by approx 20% until 1 mg on day 10 and zero dose on day 11	Study quality 1+

References of Included Studies

ZENG2005 (Published Data Only)

Zeng, X., Lei, L., Lu, Y., et al. (2005) Treatment of heroinism with acupuncture at points of the Du channel. Journal of Traditional Chinese Medicine, 25, 166-170

Characteristics of reviewed studies: Efficacy of psychosocial interventions

Comparisons Included in this Clinical Question

Detoxification + Any Psychosocial Other Than Behavioural Reinforcement
GALANTER2004
RAWSON1983
YANDOLI2002

Detoxification + Behavioural Reinforcement
BICKEL1997
HALL1979
HIGGINS1984
HIGGINS1986
KATZ2004
MCCAUL1984

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BICKEL1997 Study Type: RCT (randomised controlled trial) Study Description: Patients blind to buprenorphine dosage Blindness: Single blind Duration (days): Mean 180 Setting: Federally funded programme in US Notes: RANDOMISATION: Minimum likelihood allocation Info on Screening Process: Not reported	n= 39 Age: Mean 34 Range 19-45 Sex: 25 males 14 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - did not meet FDA guidelines for methadone treatment - age <18 - psychosis, dementia, or medical disorders contraindicating buprenorphine - pregnant Baseline: GROUPS: CM + community reinforcement approach / TAU) Previous opiate treatment: 79% / 80% Years of regular use: 8.8 / 11.4 Age first use: 20.4 / 21.0 Preferred route: IV 63% / 65%, oral 21% / 20%, nasal 16% / 15% Polydrug dependence: Alcohol 32% / 26%, cocaine 26% / 35% ASI Drug: 0.35 / 0.41	**Data Used** Urinalysis Abstinence: longest period Completion Notes: Urinalysis for other drugs: participant defined as positive for any positive sample throughout study	**Group 1 N= 19** Opiate partial agonist: buprenorphine with outpatient - Initiated and stabilised over first week on 2, 4 or 8mg/70kg depending on level of opiate usage, withdrawal symptoms and level of intoxication; maintained on same dose for 72/42/7 days respectively. Tapered to 0 over remainder of study (~ -10% per 5 days) Psychosocial: CRA (community reinforcement apprch) - 1 hour 2-3 times weekly; individual counselling on relationships and employment, drug use, and assistance in developing recreational activities. Behavioural contract with significant other. Voucher reinforcement for three verified activities per week. Psychosocial: CM (contingency management) - 1st opiate -ve sample earned $3.63, each successive -ve sample raised voucher value by $0.125. $5 bonus for 3 consecutive -ve samples. Failure to submit -ve sample reset value to initial level. Vouchers redeemed for material reinforcers at own request **Group 2 N= 20** Opiate partial agonist: buprenorphine with outpatient - Initiated and stabilised over first week on 2, 4 or 8mg/70kg depending on level of opiate usage, withdrawal symptoms and level of intoxication; maintained on same dose for 72/42/7 days respectively. Tapered to 0 over remainder of study (~ -10% per 5 days) Psychosocial: TAU (treatment as usual) - Weekly 37-min sessions addressing compliance and rehabilitation based on standard MMT clinic practice. Counsellors suggested or devised plans to address decreasing drug use, and employment/accommodation needs	Study quality 1+
GALANTER2004				

Study Type: RCT (randomised controlled trial) Study Description: Blinding of medication dose Type of Analysis: Per protocol Blindness: Single blind Duration (days): Mean 126 Setting: New York, US Info on Screening Process: 86 interviewed, 20 ineligible (polydrug dependence, DSM-IV psychiatric disorder, lack of suitable collateral) so 66 randomised	n= 66 Age: Mean 36 Sex: 50 males 16 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age outside range 21-65 - unable to bring a drug-free family member or friend to join treatment - major Axis I psychiatric disorders Notes: PRIMARY DIAGNOSIS: Heroin dependence ETHNICITY: 59% White, 24% Hispanic, 12% Black, 5% Asian Baseline: Living with family or friends: 77% Years of heroin use: 12.3 Previous treatment for heroin addiction: 73% Previous MMT: 30%	**Data Used** Abstinence: past 3 negative urine samples Urinalysis Completion	**Group 1 N= 31** Opiate partial agonist: buprenorphine-naloxone with outpatient - As per network therapy group Psychosocial: TAU (treatment as usual) - Response to medication monitored based on set procedures.Therapist developed and fostered alliance with the patient, but focus was on the effect of medication. No specific behavioural strategies were prescribed **Group 2 N= 33** Opiate partial agonist: buprenorphine-naloxone with outpatient - Sublingual buprenorphine-naloxone. Initiated at 8 mg, increased to 16 mg on day 2, then maintained through week 5. Ten-week taper phase began in week 6, with dose reduced down to 8 mg by end of week 9 and 0 by end of week 15 Symptomatic - Clonidine and trazodone prescribed on per patient basis as required Psychosocial: FT (family therapy) - Network therapy based on Galanter manual. Focused on training network members to provide supportive environment for patients' adherence to abstinence from illicit opiates. Twice weekly 30-min sessions over 18 weeks, one of which was an individual session	Study quality 1+
HALL1979 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Open Duration (days): Mean 16 Setting: Outpatient methadone clinic in US Notes: RANDOMISATION: No details Info on Screening Process: 85 approached, 4 refused consent so 81 enrolled and randomised	n= 81 Age: Mean 28 Sex: 53 males 28 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT Exclusions: None reported Notes: ETHNICITY: 53% White, 12% Black, 24% Hispanic Baseline: None reported	**Data Used** Urinalysis Completion	**Group 1 N= 40** Opiate agonist: methadone with outpatient - 16-day taper: day 1, 40 mg divided into two doses; day 2, 20 mg; from day 3, 5 mg decrease every other day with final dose of 5 mg on day 16 Psychosocial: CM (contingency management) with outpatient - Payment for drug-free urines on Mon, Wed and Fri. Sequence of payments: $10, $6, $4, $6 and $10. $15 upon detoxification completion (defined as returning for methadone dose on day 16). Brief (5-min) conversation about treatment progress once a week **Group 2 N= 41** Psychosocial: NCM (non-contingent management) with outpatient - $1 for each urine given Opiate agonist: methadone with outpatient - As per CM group	Study quality 1+
HIGGINS1984 Study Type: RCT (randomised controlled trial) Study Description: Participants and experimenters blind to methadone dose (administered in cherry syrup) Blindness: Double blind Duration (days): Mean 70	n= 27 Age: No information Sex: all males Diagnosis: 100% opiate dependence by clinical assessment	**Data Used** Urinalysis Retention: duration in treatment Completion	**Group 1 N= 9** Opiate agonist: methadone - For weeks 1 6, tapered from 30 mg to 0 mg. Dose increases still available weeks 7-8, then stopped beginning of week 9 and the clinic dose was raised to 15 mg. This was then reduced again to 0 mg in 5 mg	Study quality 1+

Setting: Latter part of 13-week detoxification programme Info on Screening Process: 35 enrolled in detoxification; 28 provided >=50% opiate-free urines: eligible and randomised	Exclusions: Failing to provide >=50% opiate-free urines during first three weeks of detoxification Baseline: Not reported		decrements every 3 days Psychosocial: CM (contingency management) - Allowed to increase methadone dose by 5, 10, 15 or 20 mg or a daily basis, only if most recent urine sample was opiate negative **Group 2 N= 8** Opiate agonist: methadone - As per CM group Psychosocial: NCM (non-contingent management) - Allowed dose increases regardless of urinalysis results **Group 3 N= 10** Opiate agonist: methadone - For weeks 1 6, tapered from 30 mg to 0 mg. Remained at 0 mg throughout rest of study period, with no dose increases allowed throughou	
HIGGINS1986 Study Type: RCT (randomised controlled trial) Study Description: Methadone administered in cherry syrup throughout. Participants had no information about dosing schedules Type of Analysis: ITT (LOCF) Blindness: Double blind Duration (days): Mean 70 Setting: Outpatient detoxification programme, US Notes: RANDOMISATION: No details Info on Screening Process: 58 enrolled onto 13-week detoxification, 8 left study during screening phase and 11 ineligible; 38 randomised	n= 39 Age: Mean 32 Sex: no information Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - failing to provide 50% or more opiate negative urines during screening phase - no physical evidence for recent intravenous drug use Notes: ETHNICITY: 49% Black, 51% White Baseline: GROUPS: CM / non-contingent management / control Years of continuous opiate use: 8.5 / 10.4 / 9.0 Parole, probation or pending trial: 3 / 3 / 6 Employed: 38% / 46% / 54%	**Data Used** Withdrawal severity Retention: duration in treatment Abstinence: endpoint Urinalysis Notes: LOCF for urinalysis only	**Group 1 N= 13** Opiate agonist: methadone. Mean dose 30 mg - Tapered from 30 mg to 0 mg over 7 weeks (in alternate 2 mg and 3 mg steps), cherry syrup only for remaining weeks. Patients reported to clinic daily for supervised methadone and thrice-weekly urinalysis Psychosocial: CM (contingency management) - In addition to clinic dose, allowed to increase dose by 5, 10, 15 or 20 mg on a daily basis throughout study period, only if most recent urine sample was opiate negative **Group 2 N= 13** Opiate agonist: methadone. Mean dose 30 mg - As per CM group Psychosocial: NCM (non-contingent management) - In addition to clinic dose, allowed to increase dose by 5, 10, 15 or 20 mg on a daily basis throughout study period regardless of urine results **Group 3 N= 13** Opiate agonist: methadone. Mean dose 30 mg - As per CM group, except no dose increases allowed (i.e. methadone dose was 0 mg from week 7 onwards)	During 3-week screening phase, all participants were stabilised onto 30 mg methadone Study quality 1+
KATZ2004 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT (missing urines as +ve) Blindness: Open Duration (days): Mean 5 Followup: 2 days Setting: Outpatient buprenorphine detox programme in US Notes: RANDOMISATION: Weekly intake cohorts randomised into either condition (total 40 cohorts randomised). Reported no significant clustering of outcomes Info on Screening Process: 646 approached >	n= 211 Age: Mean 34 Sex: 82 males 129 females Diagnosis: 100% opiate dependence Exclusions: None reported Notes: PRIMARY DIAGNOSIS: 'opiate abusers' entering detox Baseline: (GROUPS: CM / NCM) Opiate -ve urines at intake: 8% / 7% Cocaine -ve urines at intake: 39% / 33%	**Data Used** Opiate use Cocaine use	**Group 1 N= 109** Psychosocial: group therapy with outpatient - Daily group counselling Opiate partial agonist: buprenorphine with outpatient. Mean dose 0.3mg/day - Intramuscular buprenorphine administered for 4 days Psychosocial: TAU (treatment as usual) with outpatient	Study quality 1+

246 gave consent - 35 excluded from analysis (15 no urine samples, 12 pilot participants, 4 no indication of opiate use throughout study, 4 violated protocol) > 211 randomised			Psychosocial: CM (contingency management) with outpatient - $100 voucher for opiate and cocaine -ve urine samples at end of detoxification. Exchangeable for gift certificates from area retailers or for services consistent with drug-free lifestyle **Group 2 N= 102** Psychosocial: group therapy - As per CM group Psychosocial: NCM (non-contingent management) - Randomly selected participants received $100 voucher. Proportion of participants selected equal to proportion of participants receiving voucher in CM condition Opiate partial agonist: buprenorphine - As per CM group Psychosocial: TAU (treatment as usual)	
MCCAUL1984 Study Type: RCT (randomised controlled trial) Study Description: Participants and experimenters blind to methadone dose throughout (administered in cherry syrup) Blindness: Double blind Duration (days): Mean 70 Setting: US Notes: RANDOMISATION: No details Info on Screening Process: 33 enrolled in 13-week outpatient detox, 20 provided 50% opiate negative urines during screening phase: eligible and randomised	n= 20 Age: Mean 30 Sex: no information Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - no physical evidence of recent intravenous drug use - failing to provide three consecutive opiate negative urines Notes: PRIMARY DIAGNOSIS: Illicit opiates, not currently in treatment ETHNICITY: 60% Black, 40% White Baseline: GROUPS: CM / control Years of opiate use: 7.0 / 8.1 Parole or probation: 30% / 30% Employed: 30% / 30%	**Data Used** Withdrawal severity Retention: duration in treatment Abstinence: during treatment Abstinence: longest period Urinalysis	**Group 1 N= 10** Opiate agonist: methadone. Mean dose 30 mg - Tapered from 30 mg to 0 mg over 6 weeks (alternating 2 mg / 3 mg reduction every 4 days), cherry syrup for last 4 weeks. Standard clinic procedures with twice weekly urinalysis, symptomatology questionnaire and weekly counselling Psychosocial: CM (contingency management) - $10 and a take-home dose for each opiate-free urine specimen provided on Monday or Friday **Group 2 N= 10** Opiate agonist: methadone. Mean dose 30mg - As per CM group Psychosocial: NCM (non-contingent management) - $5 reward for each urine sample provided regardless of result	Study quality 1+
RAWSON1983 Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 21 Followup: 6 months Setting: Los Angeles, US Notes: RANDOMISATION: Random numbers table Info on Screening Process: Not reported	n= 50 Age: Mean 30 Range 18-54 Sex: 33 males 17 females Diagnosis: 100% opiate dependence Exclusions: None reported Notes: PRIMARY DIAGNOSIS: Seeking admissions to 21-day detoxification Baseline: Years of heroin dependence: 8.8 Previous detoxification attempts: 4.0	**Data Used** Entry to further treatment Abstinence: during treatment Completion Relapse Retention: in treatment at follow-up Retention: duration in treatment	**Group 1 N= 25** Opiate agonist: methadone with outpatient - Initiated on 35 mg then tapered systematically to 0 over 21 days **Group 2 N= 25** Psychosocial: individual therapy with outpatient - Individual drug counselling as used by Woody. Mandatory session on day 2, subsequent voluntary sessions during wks 2-3. 15-20min sessions with assessment of patient's needs and provision/information about services meeting those needs Opiate agonist: methadone with outpatient - As per control group	Study quality 1++
YANDOLI2002				

Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 365 Setting: Drug dependency clinic, London Notes: RANDOMISATION: Participants cohabiting with another drug user were both placed in the same treatment group. No other details. Info on Screening Process: 423 presented for treatment; 119 eligible and agreed to include family members if required	n= 119 Age: Mean 28 Sex: 75 males 44 females Diagnosis: 100% opiate dependence Exclusions: - history of psychiatric treatment - age <18 - alcohol dependent - opiate use <6 months - did not agree to being seen with partner/family during treatment	**Data Used** Mortality Opiate use Retention: duration in treatment	**Group 1 N= 41** Opiate agonist: methadone - Non-negotiable reduction regime, with daily dose reduced by 5 mg every 2 weeks Psychosocial: FT (family therapy) - Structured/strategic approach based on Stanton et al. Up to 16 1-hour sessions, initally every 2 weeks then less often. Therapist worked primarily with couple (if in a relationship), but other significant relationships and family members were included **Group 2 N= 40** Opiate agonist: methadone - Flexible reduction regime, which sometimes included continuing on a stable dose or occasionally increasing dose temporarily Psychosocial: TAU (treatment as usual) - Pragmatic, supportive counselling provided by multidisciplinary team. Did not follow a clearly defined theoretical model. Open-ended course of treatment **Group 3 N= 38** Psychosocial: minimal contact - More structured, limited approach than TAU and discouraged dependency on therapist, who on day of assessment gave package of information about local services. Participants seen monthly for standardised 30-min interview for up to 12 months Opiate agonist: methadone - Non-negotiable regime as per FT group	Planned duration of treatments not reported - assumed study duration of 1 year Study quality 1+

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
ELMOGHAZY1989	Intervention not relevant

References of Included Studies

BICKEL1997 (Published Data Only)

Bickel, W.K., Amass, L., Higgins, S.T., et al. (1997) Effects of adding behavioral treatment to opioid detoxification with buprenorphine. Journal of Consulting and Clinical Psychology, 65, 803-810.

GALANTER2004 (Published Data Only)

Galanter, M., Dermatis, H., Glickman, L., et al. (2004) Network therapy: decreased secondary opioid use during buprenorphine maintenance. Journal of Substance Abuse Treatment, 26, 313-318.

HALL1979 (Published Data Only)

Hall, S.M., Bass, A., Hargreaves, W.A., et al. (1979) Contingency management and information feedback in outpatient heroin detoxification. Behavior Therapy, 10, 443-451.

HIGGINS1984 (Published Data Only)

Higgins, S.T., Stitzer, M.L., Bigelow, G.E., et al. (1984) Contingent methadone dose increases as a method for reducing illicit opiate use in detoxification patients. NIDA Research Monograph, 55, 178-184.

HIGGINS1986 (Published Data Only)

Higgins, S.T., Stitzer, M.L., Bigelow, G.E., et al. (1986) Contingent methadone delivery: effects on illicit-opiate use. Drug and Alcohol Dependence, 17, 311-322.

KATZ2004 (Published Data Only)

Katz, E. C., Chutuape, M. A., Jones, H., et al. (2004) Abstinence incentive effects in a short-term outpatient detoxification program. Experimental & Clinical Psychopharmacology, 12, 262-268.

MCCAUL1984 (Published Data Only)

McCaul, M.E., Stitzer, M.L., Bigelow, G.E., et al. (1984) Contingency management interventions: effects on treatment outcome during methadone detoxification. Journal of Applied Behavior Analysis, 17, 35-43.

RAWSON1983 (Published Data Only)

Rawson, R.A., Mann, A.J., Tennant, F.S.J., et al. (1983) Efficacy of psychotherapeutic counselling during 21-day ambulatory heroin detoxification. Drug and Alcohol Dependence, 12, 197-200.

YANDOLI2002 (Published Data Only)

Yandoli, D., Eisler, I., Robbins, C., et al. (2002) A comparative study of family therapy in the treatment of opiate users in a London drug clinic. Journal of Family Therapy, 24, 402-422.

References of Excluded Studies

ELMOGHAZY1989

Elmoghazy, E., Johnson, B.D. & Alling, F.A. (1989) A pilot study of a neuro-stimulator device vs. methadone in alleviating opiate withdrawal symptoms. NIDA Research Monograph, 95, 388-389.

Characteristics of reviewed studies: Treatment settings for opioid detoxification

Comparisons Included in this Clinical Question

Inpatient Versus Outpatient
DAY2006
GOSSOP1986
WILSON1975

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
DAY2006 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): No information Followup: 6months Setting: UK	n= 71 Age: No information Sex: No information Diagnosis: 100% opiate dependence	**Data Used** Completion	**Group 1 N= 37** Detoxification with inpatient **Group 2 N= 34** Detoxification with outpatient	Study Quality 1+
GOSSOP1986 Study Type: Non-randomised controlled trial Blindness: Open Duration (days): Mean 21 Setting: Drug-dependence clinic, UK Info on Screening Process: All participants voluntary patients asking to be withdrawn	n= 60 Age: Mean 26 Sex: 45 males 15 females Diagnosis: 78% opiate dependence Notes: Primary dependence = heroin 78% Methadone dependence:18% Codeine/dihydrocodeine: 3% 31 intravenous users, 17 smoked heroin, 12 oral users, 39 used 'other' non-opiate drugs Baseline: Age at first use of opiates: mean 20.7 years Age at which addiction began: 22.5 years Mean use of illicit heroin: 0.25-0.5 g	**Data Used** Urinalysis Notes: Results did not describe sub-divisions of those who expressed a preference for inpatient or outpatient treatment compared to those who had no preference. The analysis simply compares inpatient with outpatient treatment	**Group 1 N= 20** Opiate agonist: methadone with inpatient - Those in the inpatient group underwent withdrawal with oral methadone over a period of 21 days. The dose of methadone was reduced daily using a linear (equal dose) reduction model **Group 2 N= 40** Opiate agonist: methadone with outpatient - Patients received an equal dose of methadone as those in the inpatient group. This was reduced on a daily basis using a linear (equal dose) reduction model. Weekly attendance at clinic entailed counselling and support by psychiatrist	Study quality 1+
WILSON1975 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Open Duration (days): Mean 10 Setting: US, inpatient versus outpatient detoxification Info on Screening Process: Numbers randomised and numbers who refused treatment not known. 40 included in analysis	n= 40 Age: Mean 22 Sex: Diagnosis: 100% opiate dependence Exclusions: - no evidence of physical dependence - no evidence of current drug use through urinalysis, or clinical evidence of withdrawal Notes: Participants 'tended to be' white, single and male Baseline: 'Most' had abused alcohol, barbiturates, amphetamines and hallucinogens as well as heroin First detoxification attempt: almost 75%	**Data Used** Urinalysis Opiate use Completion Retention: duration in treatment	**Group 1 N= 10** Opiate agonist: methadone with inpatient - In an open acute psychiatric ward, followed 'usual narcotic detoxification procedure' with the single limitation that methadone dose <40 mg in any 24-hour period **Group 2 N= 30** Opiate agonist: methadone with outpatient - Supervised dose daily for 10 days (divided dose for first 3 days). Initial dose 10-20mg, stabilising at max 40mg on day 2 or 3. Dosage individualised but no more than 30mg was administered on days 4 or 5, 20mg on days 6 or 7, and 10mg on days 8, 9 or 10	All participants were offered individual counselling, invited for follow-up and provided supportive medication as indicated Study quality 1+

References of Included Studies

DAY2006 (Unpublished Data Only)

Day, E. (2006) Outpatient versus inpatient opioid detoxification: The OPIOiD study.

GOSSOP1986 (Published Data Only)

Gossop, M., Johns, A. & Green, L. (1986) Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. British Medical Journal Clinical Research Edition, 293, 103-104.

WILSON1975 (Published Data Only)

Wilson, B.K., Elms, R.R. & Thomson, C.P. (1975) Outpatient versus hospital methadone detoxification: an experimental comparison. International Journal of the Addictions, 10, 13-21.

Appendix 16a: Clinical evidence forest plots (pharmacological interventions in opioid detoxification)

Pharmacology **2**

Methadone 2
Buprenorphine 11
Alpha2 adrenergic agonists 22
Benzodiazepines 27
Detoxification dosage schedules 28
Opioid antagonist accelerated detoxification under minimal sedation 29
Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation 34

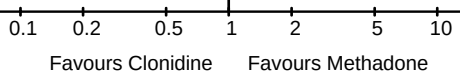
Pharmacology

Methadone

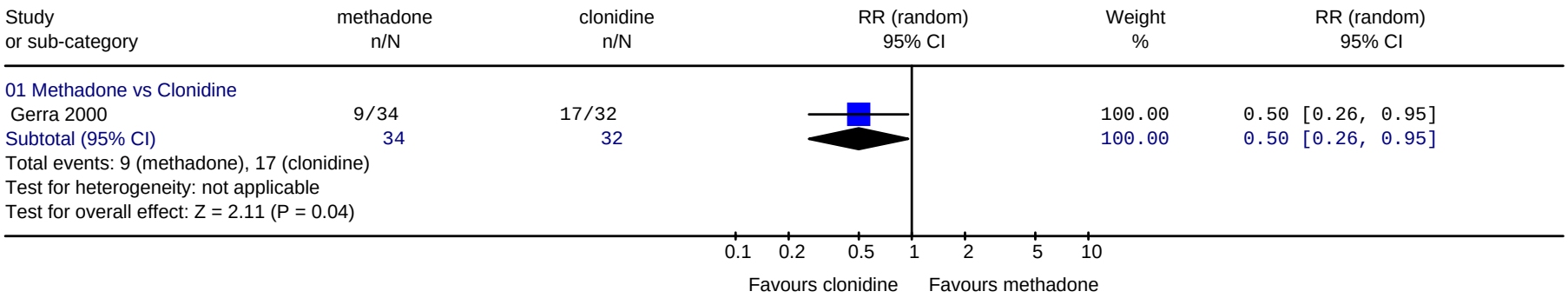
Review: DMD: Methadone
Comparison: 04 Methadone vs Clonidine
Outcome: 01 Completion of Treatment

Study or sub-category	Methadone n/N	Clonidine n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Washton 1980	6/13	4/13		15.68	1.50 [0.55, 4.10]
Kleber 1985	21/25	24/24		32.39	0.84 [0.71, 1.00]
San 1990	30/40	60/130		31.13	1.63 [1.26, 2.10]
Umbricht 2003	9/21	8/21		20.81	1.13 [0.54, 2.35]
Total (95% CI)	99	188		100.00	1.20 [0.70, 2.07]

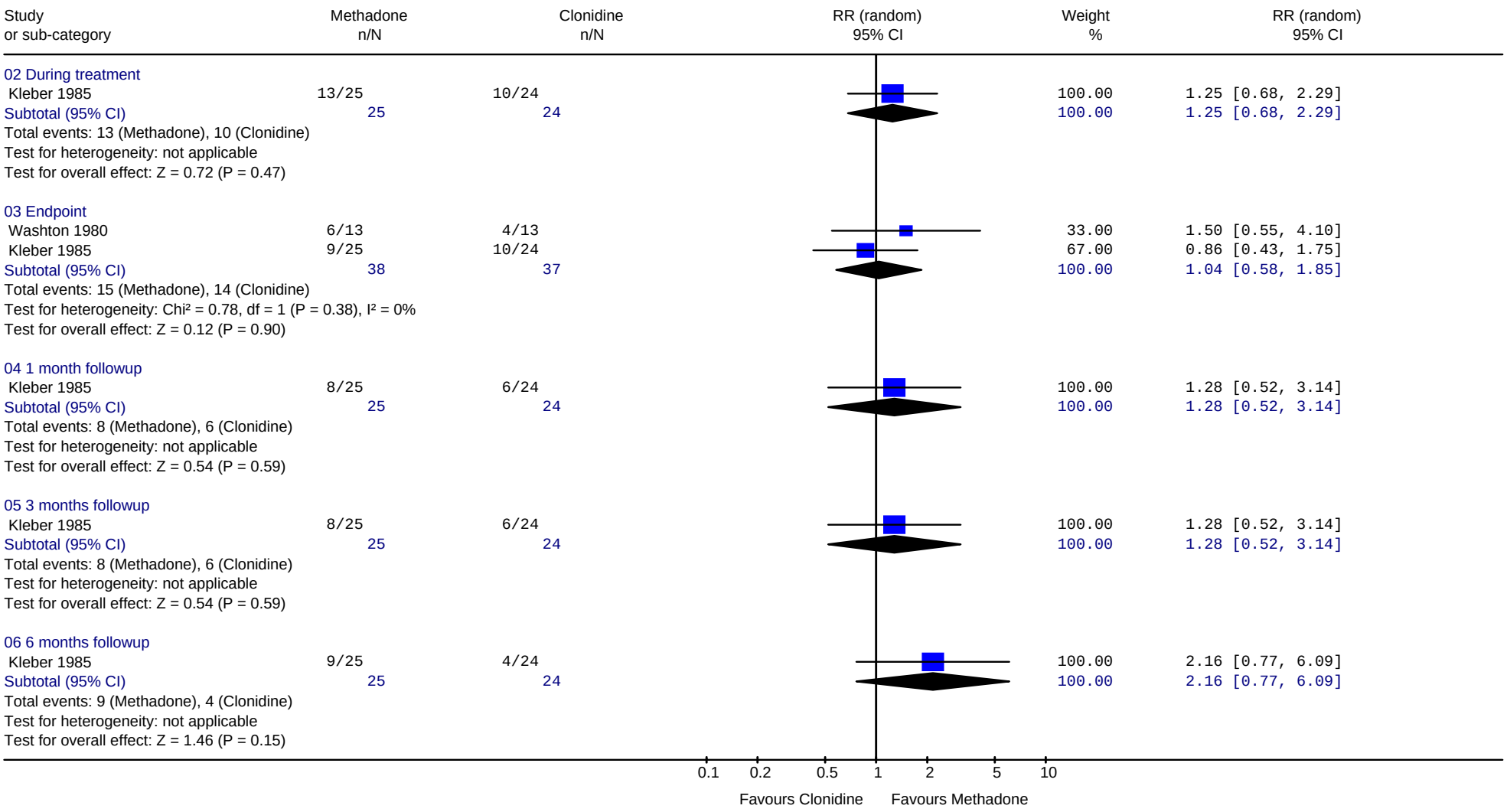
Total events: 66 (Methadone), 96 (Clonidine)
Test for heterogeneity: Chi² = 25.43, df = 3 (P < 0.0001), I² = 88.2%
Test for overall effect: Z = 0.66 (P = 0.51)



Review: DMD 1: Methadone
Comparison: 04 Methadone versus clonidine
Outcome: 02 Concordance with naltrexone maintenance (3-month follow-up)

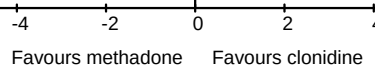


Review: DMD: Methadone
Comparison: 04 Methadone vs Clonidine
Outcome: 03 Abstinence



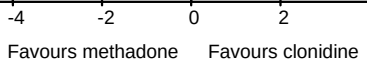
Review: DMD 1: Methadone
Comparison: 04 Methadone versus clonidine
Outcome: 05 Withdrawal: self-rated

Study or sub-category	N	methadone Mean (SD)	N	clonidine Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 Peak							
Kleber 1985	25	83.00(25.86)	25	100.00(25.86)		100.00	-0.65 [-1.22, -0.08]
Subtotal (95% CI)	25		25			100.00	-0.65 [-1.22, -0.08]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.23 (P = 0.03)							
04 Mean change from baseline							
Umbricht 2003	18	-3.30(3.68)	18	-4.70(6.73)		100.00	0.25 [-0.40, 0.91]
Subtotal (95% CI)	18		18			100.00	0.25 [-0.40, 0.91]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.45)							

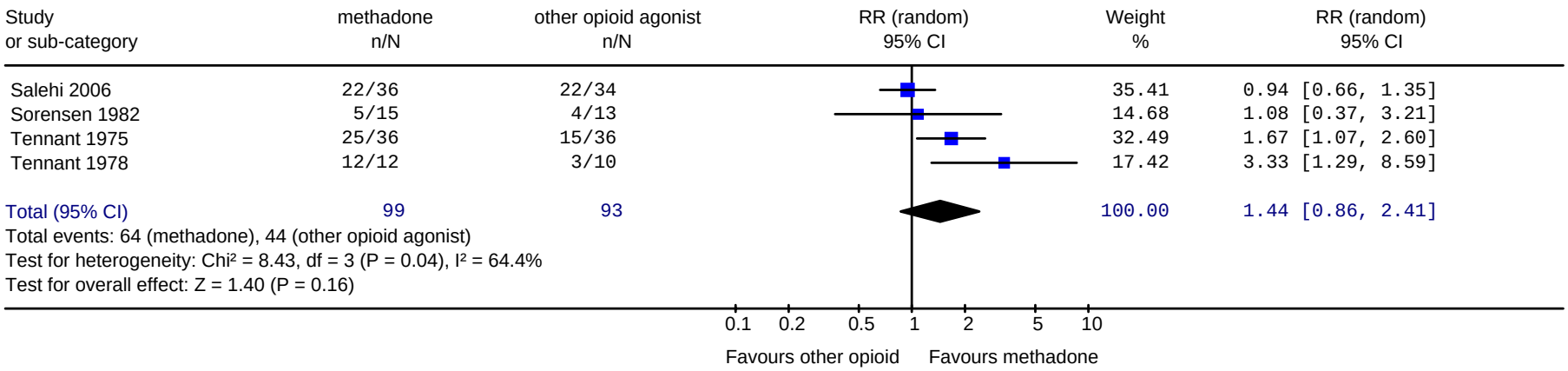


Review: DMD 1: Methadone
Comparison: 04 Methadone versus clonidine
Outcome: 06 Adverse events: side effects rating

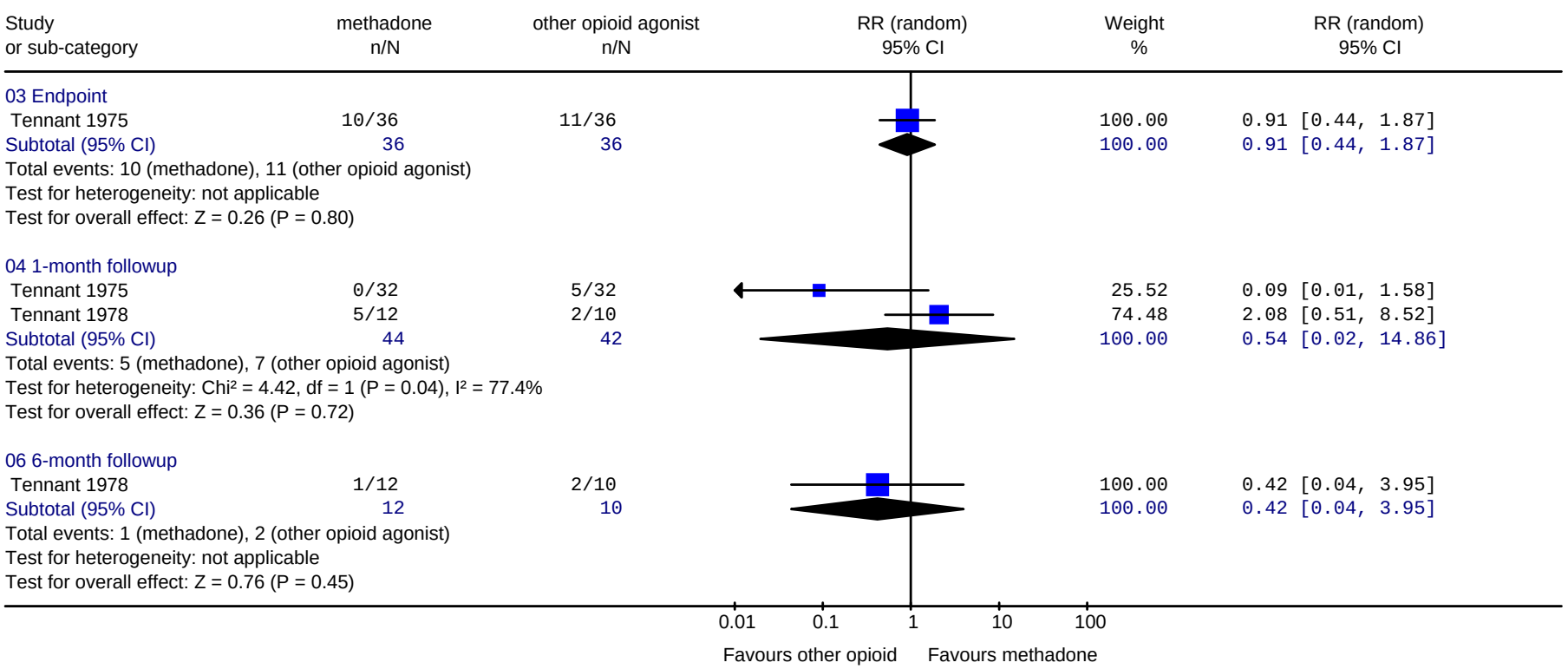
Study or sub-category	N	methadone Mean (SD)	N	clonidine Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
Jiang 1993	100	0.75(1.87)	100	2.83(2.72)		80.76	-0.89 [-1.18, -0.60]
Kleber 1985	25	11.50(4.88)	25	16.80(4.88)		19.24	-1.07 [-1.66, -0.47]
Total (95% CI)	125		125			100.00	-0.92 [-1.18, -0.66]
Test for heterogeneity: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%							
Test for overall effect: Z = 6.92 (P < 0.00001)							



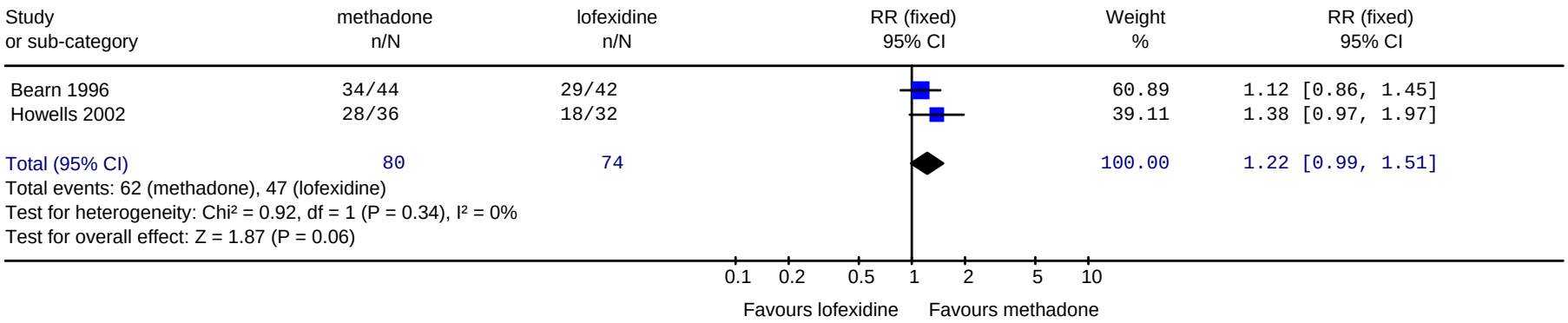
Review: DMD 1: Methadone
Comparison: 07 Methadone versus other opioid agonist (not buprenorphine)
Outcome: 01 Completion of treatment



Review: DMD 1: Methadone
Comparison: 07 Methadone versus other opioid agonist (not buprenorphine)
Outcome: 05 Abstinence

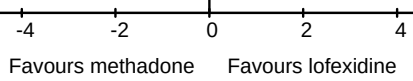


Review: DMD 1: Methadone
Comparison: 08 Methadone versus lofexidine
Outcome: 01 Completion of treatment

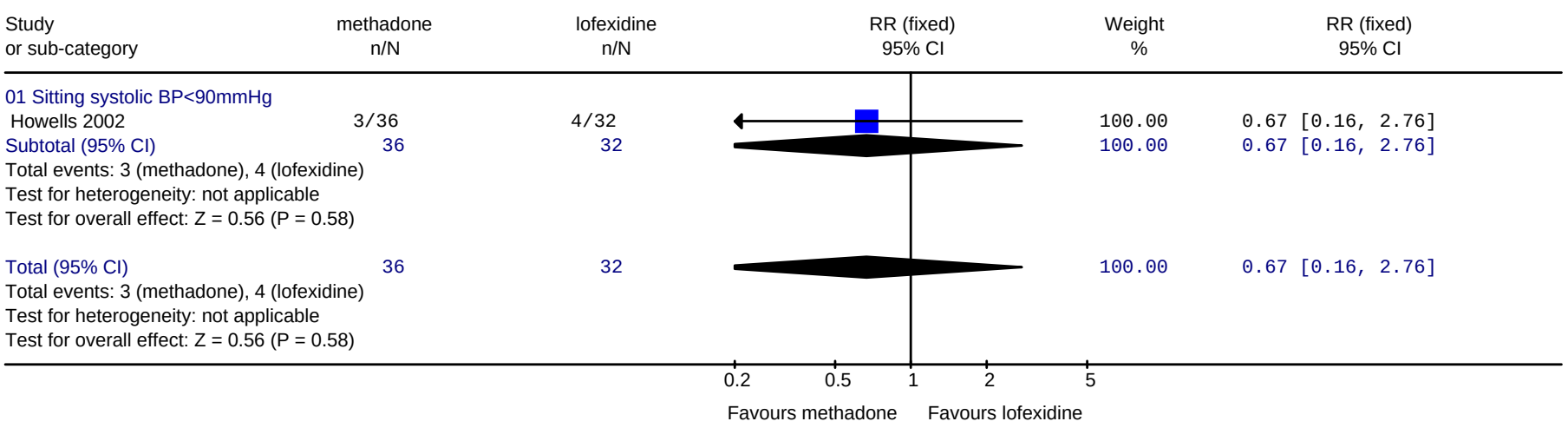


Review: DMD 1: Methadone
Comparison: 08 Methadone versus lofexidine
Outcome: 02 Withdrawal: self-rated (Short Opiate Withdrawal Scale)

Study or sub-category	N	methadone Mean (SD)	N	lofexidine Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 Peak							
Howells 2002	34	67.60(19.00)	29	69.38(22.50)		100.00	-0.09 [-0.58, 0.41]
Subtotal (95% CI)	34		29			100.00	-0.09 [-0.58, 0.41]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.74)							
02 Lowest							
Howells 2002	34	49.40(20.90)	29	50.00(18.60)		100.00	-0.03 [-0.53, 0.47]
Subtotal (95% CI)	34		29			100.00	-0.03 [-0.53, 0.47]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.12 (P = 0.91)							
03 Total/Mean							
Howells 2002	34	572.10(184.40)	29	596.10(208.30)		100.00	-0.12 [-0.62, 0.37]
Subtotal (95% CI)	34		29			100.00	-0.12 [-0.62, 0.37]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							

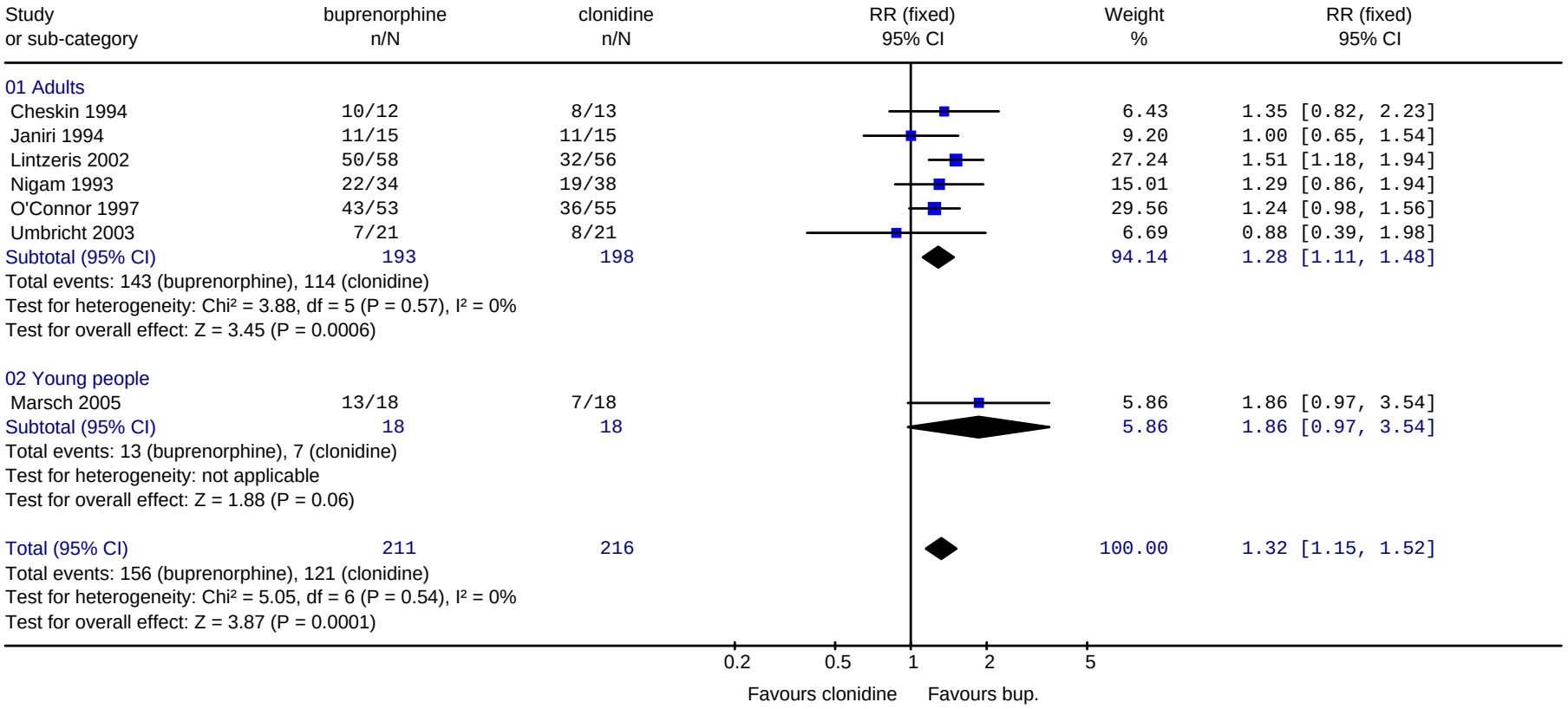


Review: DMD 1: Methadone
Comparison: 08 Methadone versus lofexidine
Outcome: 03 Hypotension

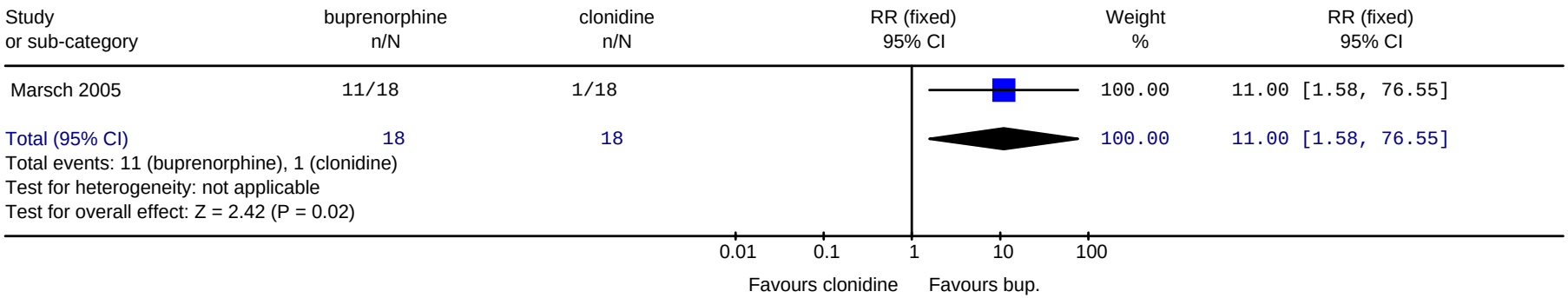


Buprenorphine

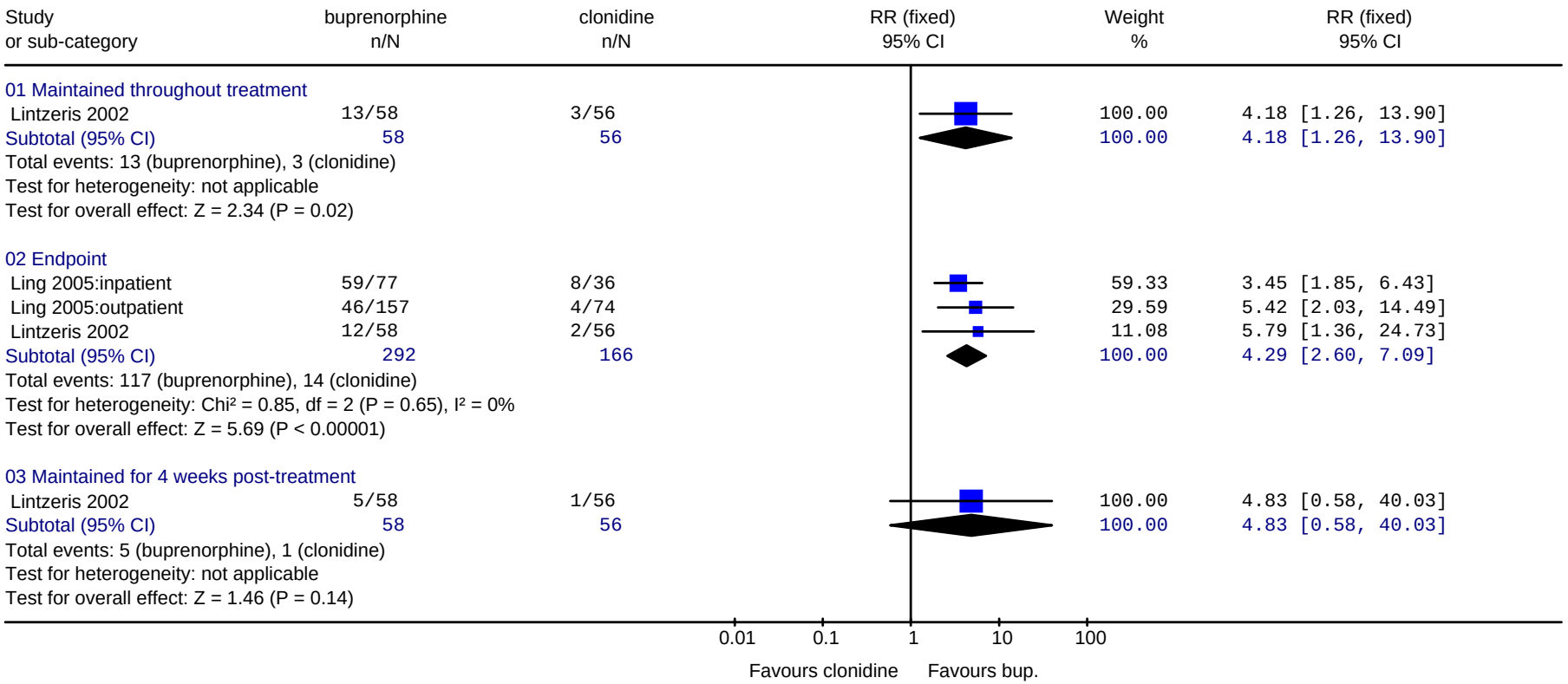
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 01 Completion of treatment



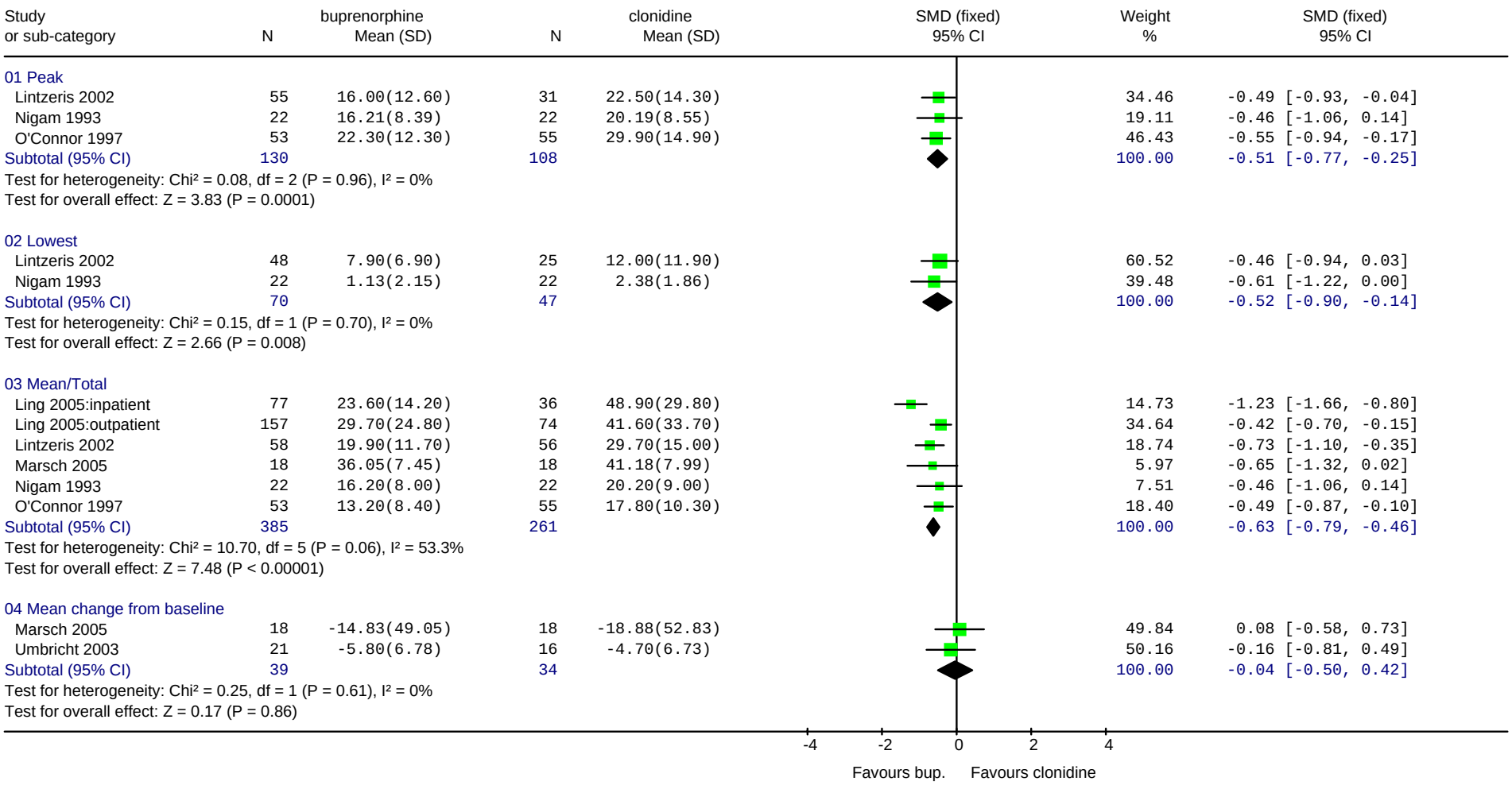
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 02 Initiated naltrexone maintenance



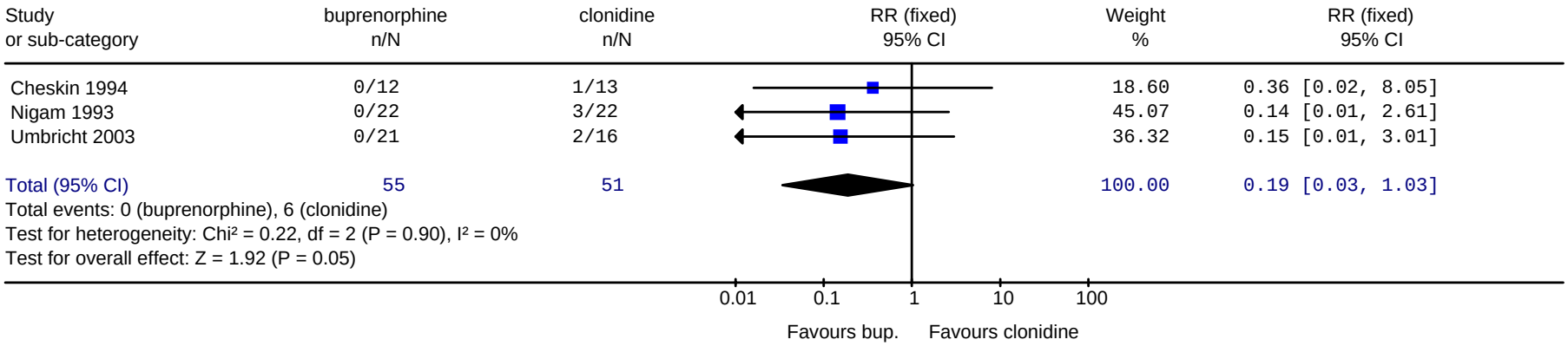
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 04 Abstinence



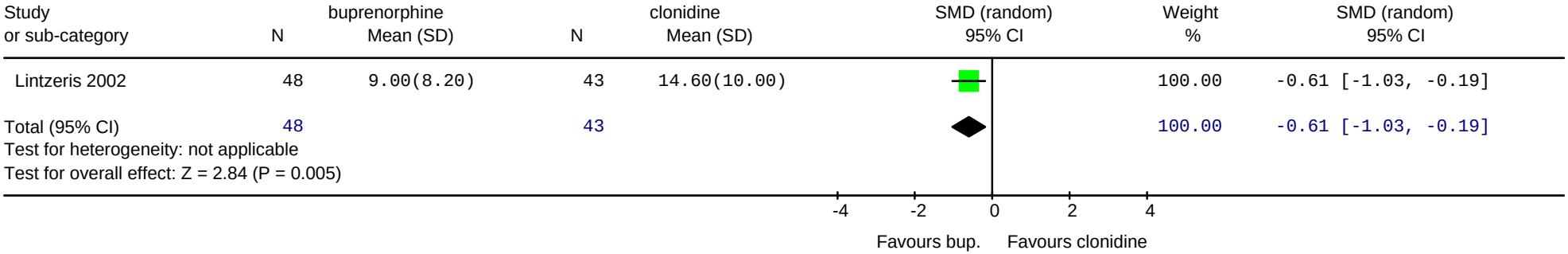
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 06 Withdrawal: subjective



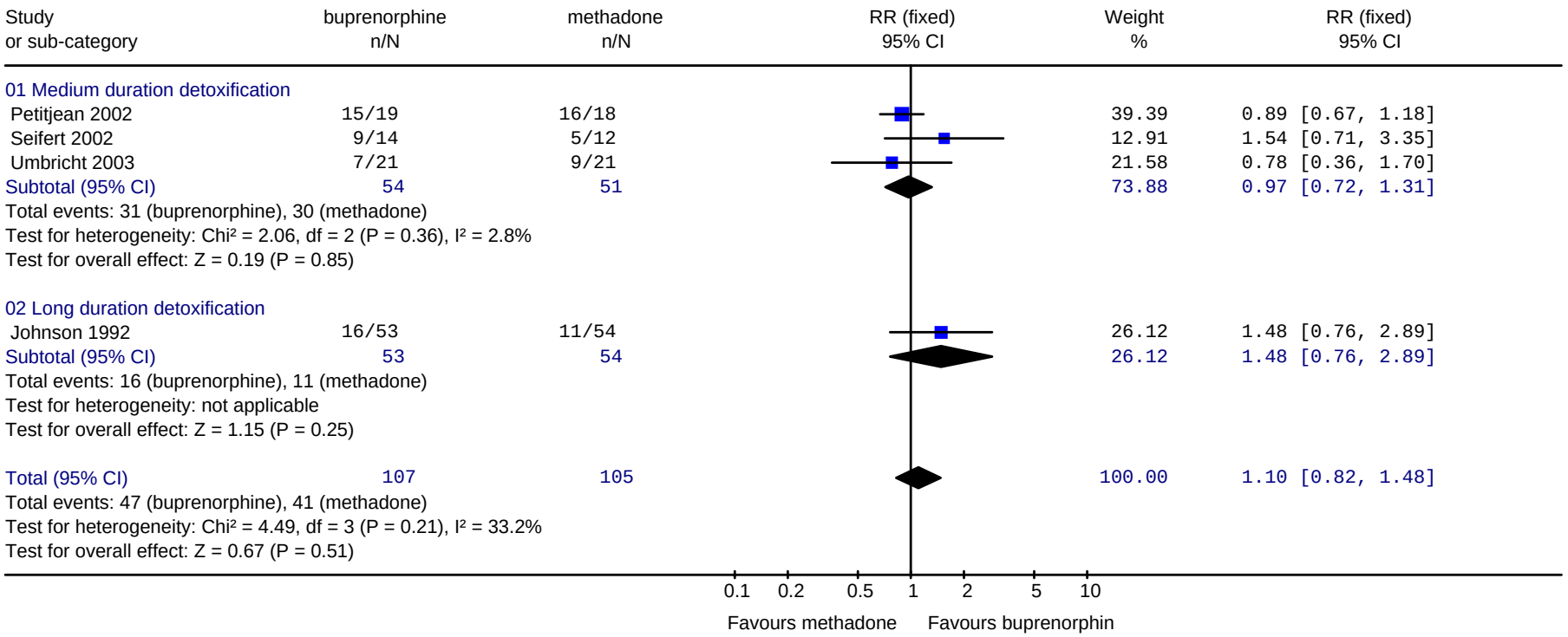
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 08 Leaving study early due to adverse events



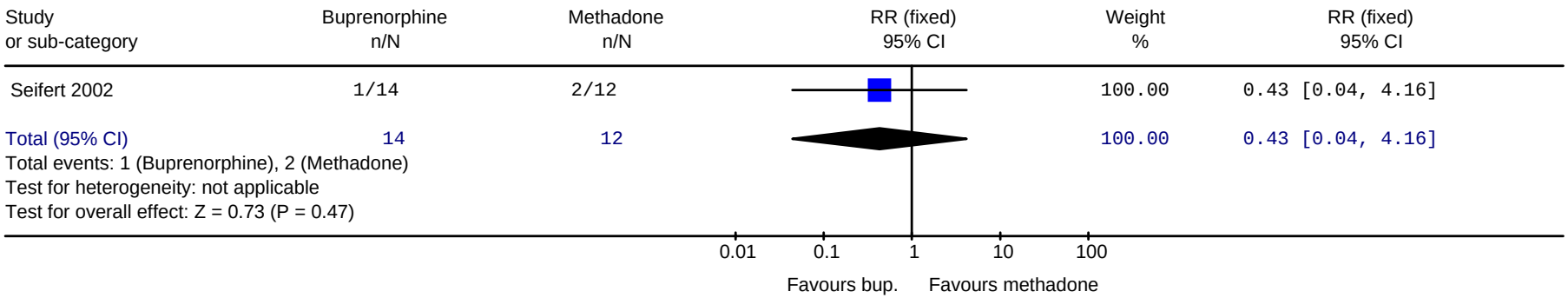
Review: DMD 2: Buprenorphine
Comparison: 02 Buprenorphine versus clonidine
Outcome: 09 Days of drug use (1-month follow up)



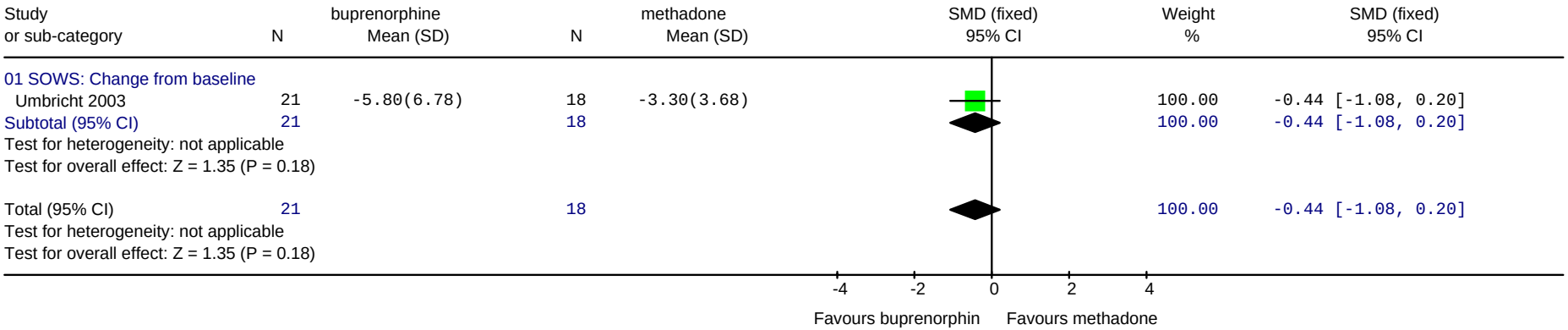
Review: DMD 2: Buprenorphine
Comparison: 03 Buprenorphine versus methadone
Outcome: 01 Completion of treatment



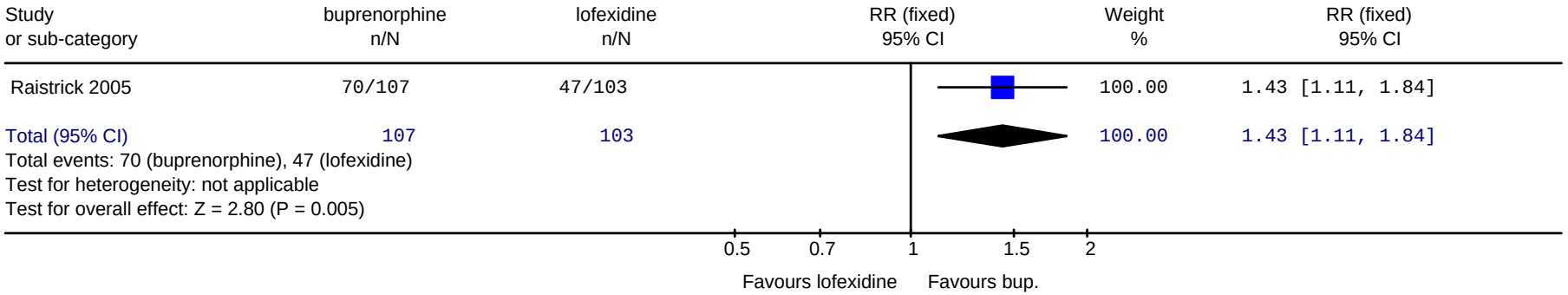
Review: DMD 2: Buprenorphine
Comparison: 03 Buprenorphine versus methadone
Outcome: 02 Relapse to opiate use (during treatment)



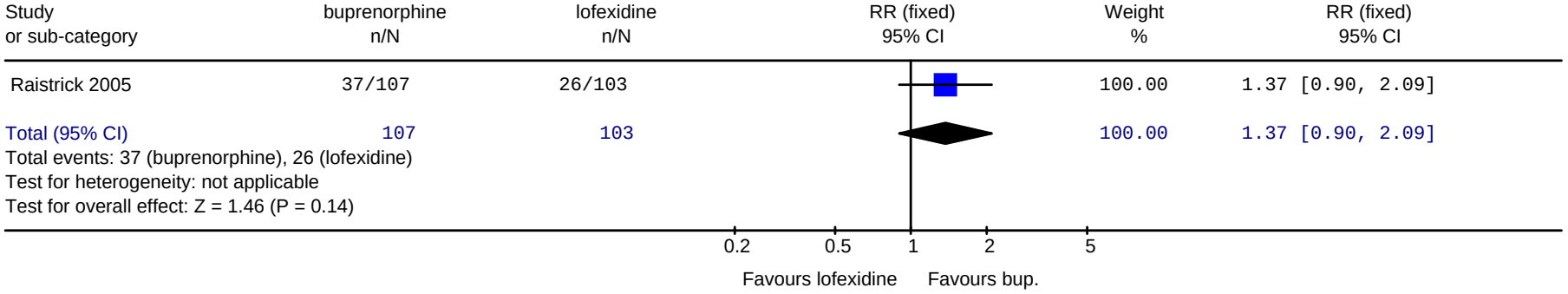
Review: DMD 2: Buprenorphine
Comparison: 03 Buprenorphine versus methadone
Outcome: 04 Withdrawal: self-rated



Review: DMD 2: Buprenorphine
Comparison: 04 Buprenorphine versus lofexidine
Outcome: 01 Completion of treatment

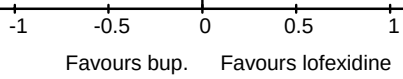


Review: DMD 2: Buprenorphine
Comparison: 04 Buprenorphine versus lofexidine
Outcome: 02 Abstinence (1-month follow-up)

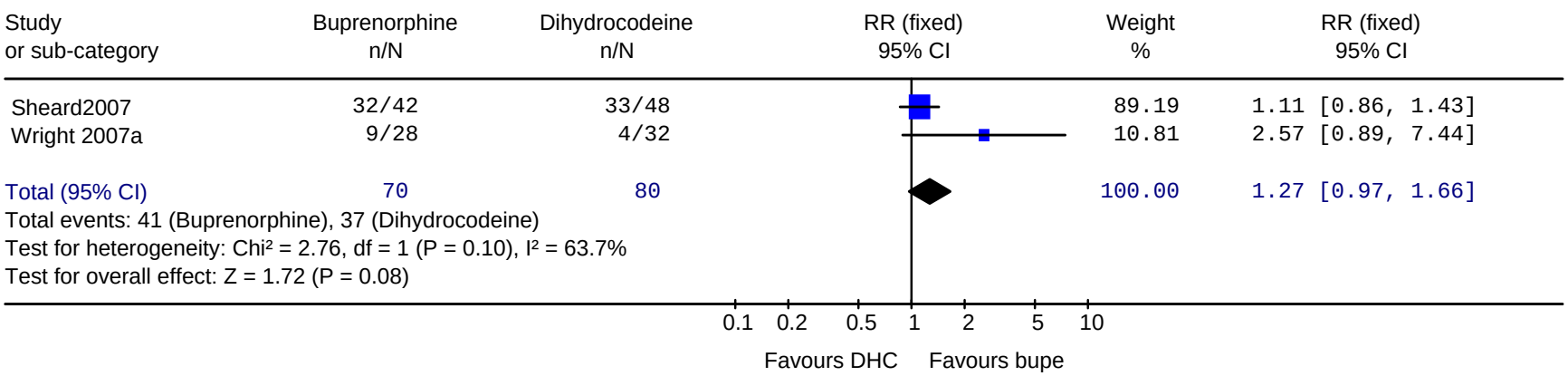


Review: DMD 2: Buprenorphine
Comparison: 04 Buprenorphine versus lofexidine
Outcome: 03 Withdrawal: self-rated

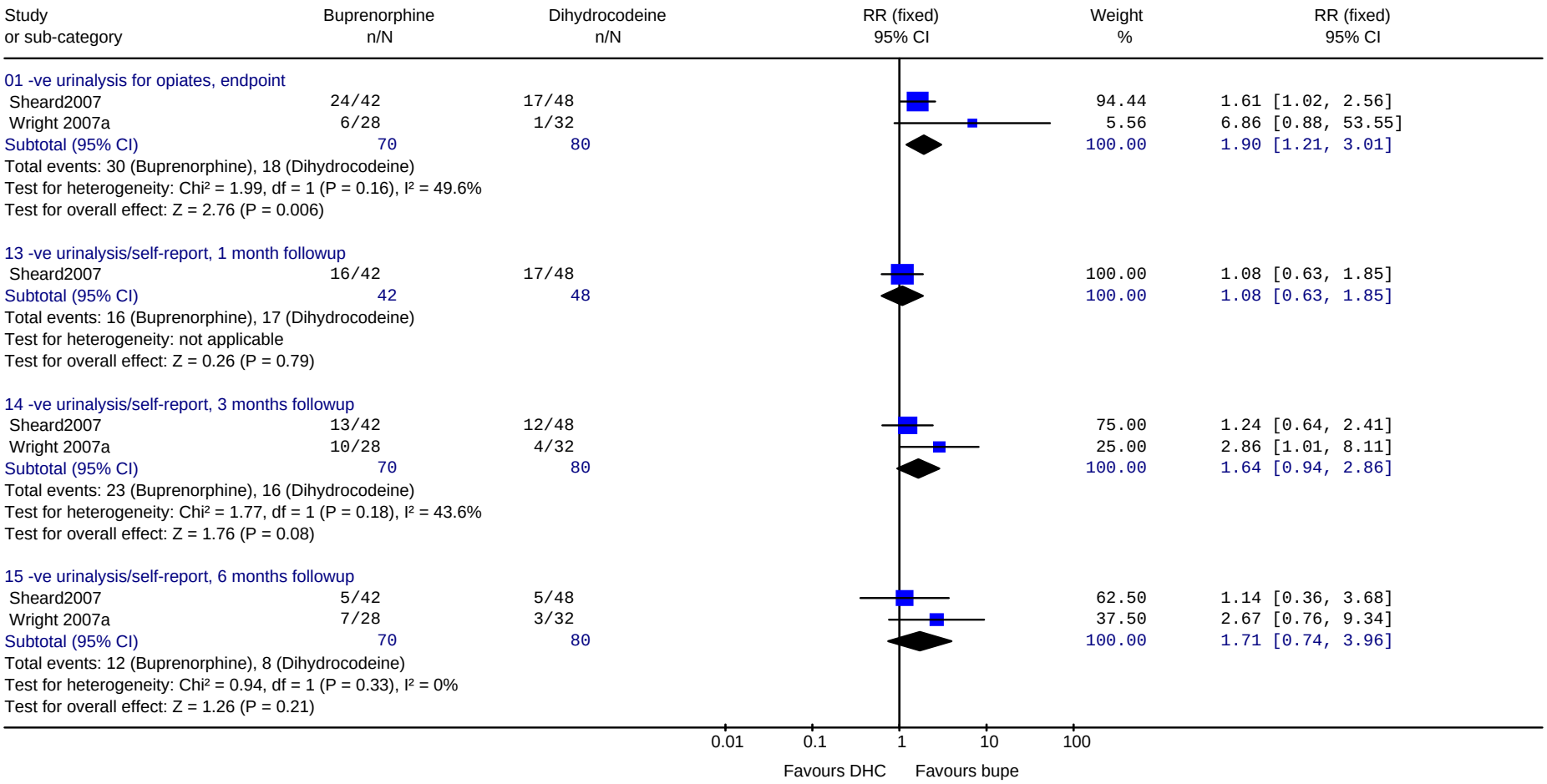
Study or sub-category	buprenorphine N	buprenorphine Mean (SD)	lofexidine N	lofexidine Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 Peak							
Raistrick 2005	106	15.60(6.99)	102	16.80(6.57)		100.00	-0.18 [-0.45, 0.10]
Subtotal (95% CI)	106		102			100.00	-0.18 [-0.45, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.27 (P = 0.20)							
02 Lowest							
Raistrick 2005	106	4.78(4.89)	102	7.43(6.48)		100.00	-0.46 [-0.74, -0.19]
Subtotal (95% CI)	106		102			100.00	-0.46 [-0.74, -0.19]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 3.28 (P = 0.001)							
03 Mean/Total							
Raistrick 2005	106	9.80(4.70)	102	12.38(5.48)		100.00	-0.50 [-0.78, -0.23]
Subtotal (95% CI)	106		102			100.00	-0.50 [-0.78, -0.23]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 3.58 (P = 0.0003)							
04 Mean change from baseline							
Raistrick 2005	103	1.66(5.79)	100	2.25(5.21)		100.00	-0.11 [-0.38, 0.17]
Subtotal (95% CI)	103		100			100.00	-0.11 [-0.38, 0.17]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							



Review: DMD: Buprenorphine
Comparison: 05 Buprenorphine vs Dihydrocodeine
Outcome: 01 Completion of treatment

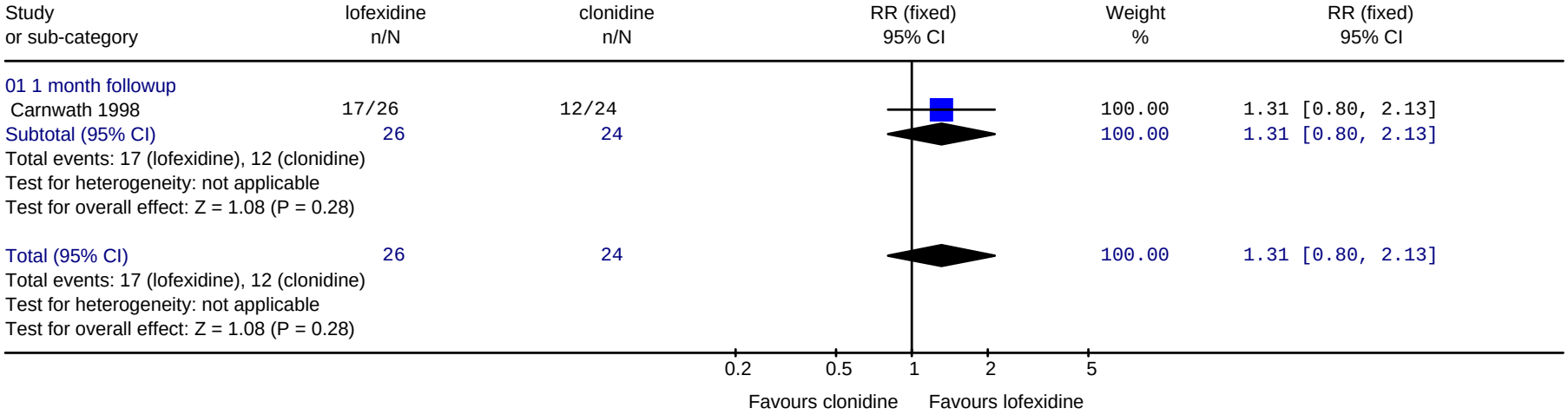


Review: DMD: Buprenorphine
Comparison: 05 Buprenorphine vs Dihydrocodeine
Outcome: 02 Abstinence (ITT)

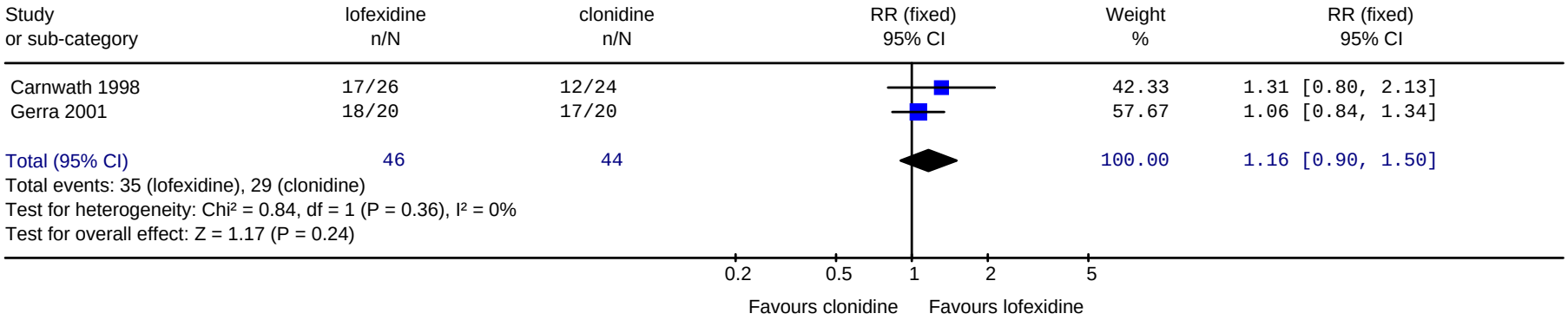


Alpha2 adrenergic agonists

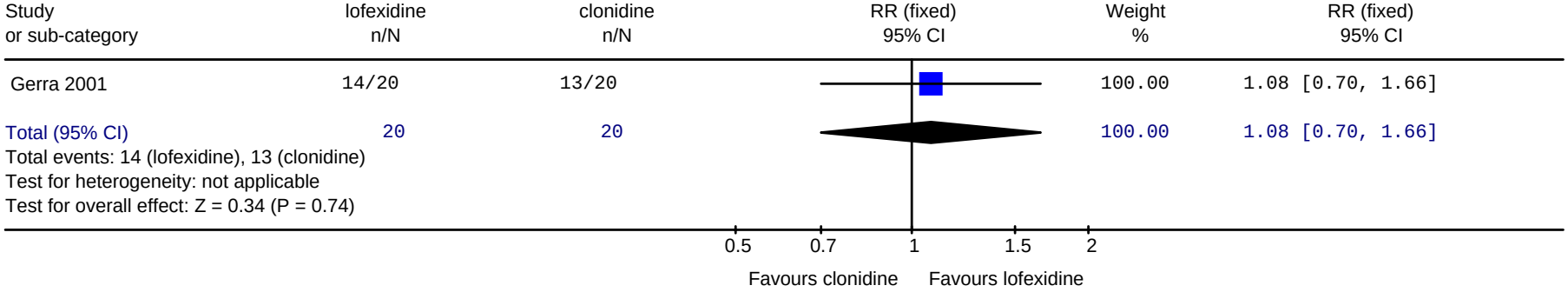
Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 03 Lofexidine versus clonidine
Outcome: 01 Abstinence



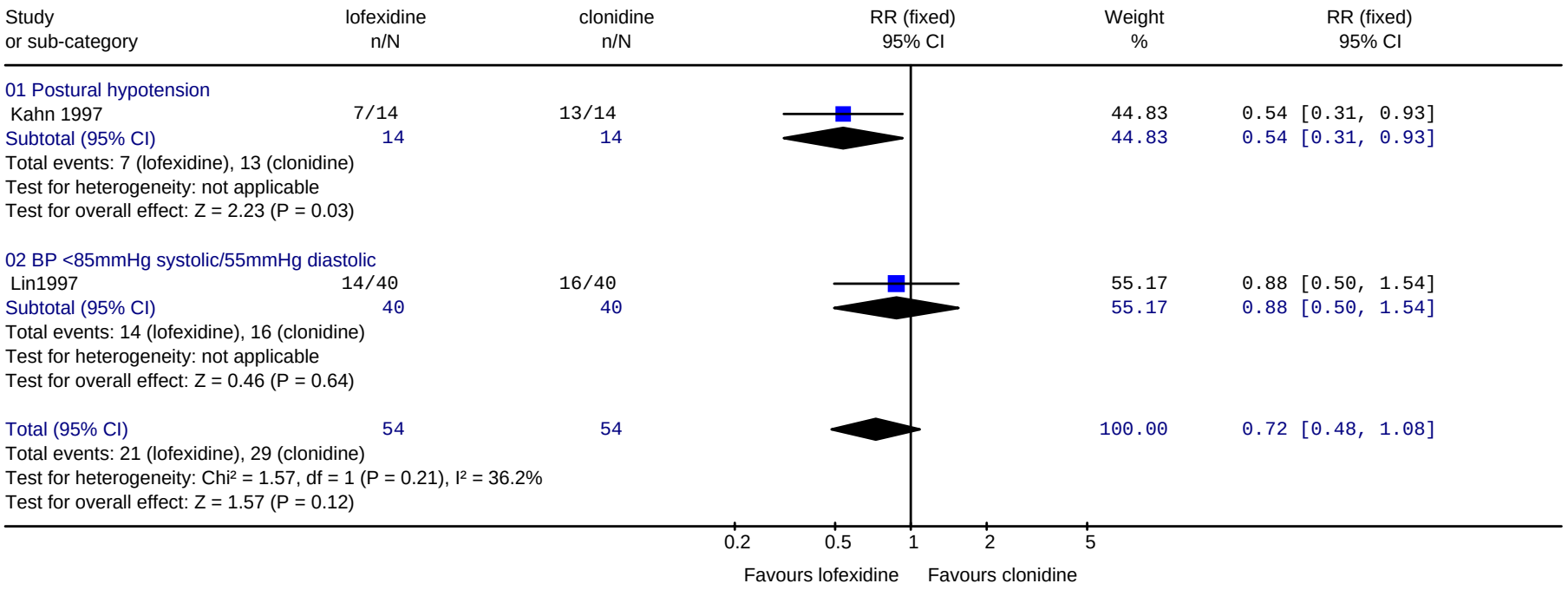
Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 03 Lofexidine versus clonidine
Outcome: 02 Completion of treatment



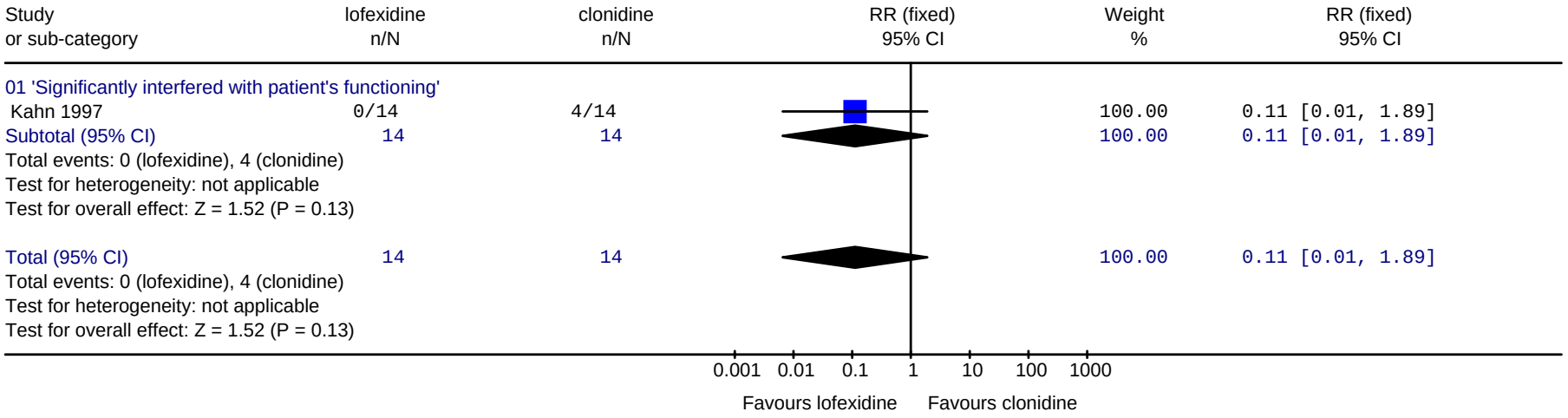
Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 03 Lofexidine versus clonidine
Outcome: 03 Induction onto naltrexone maintenance



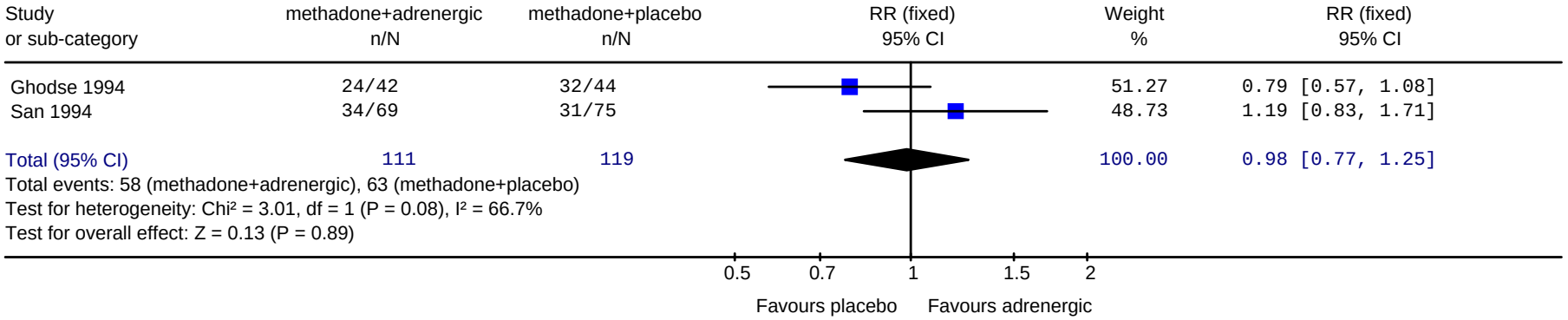
Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 03 Lofexidine versus clonidine
Outcome: 04 Adverse events: hypotension



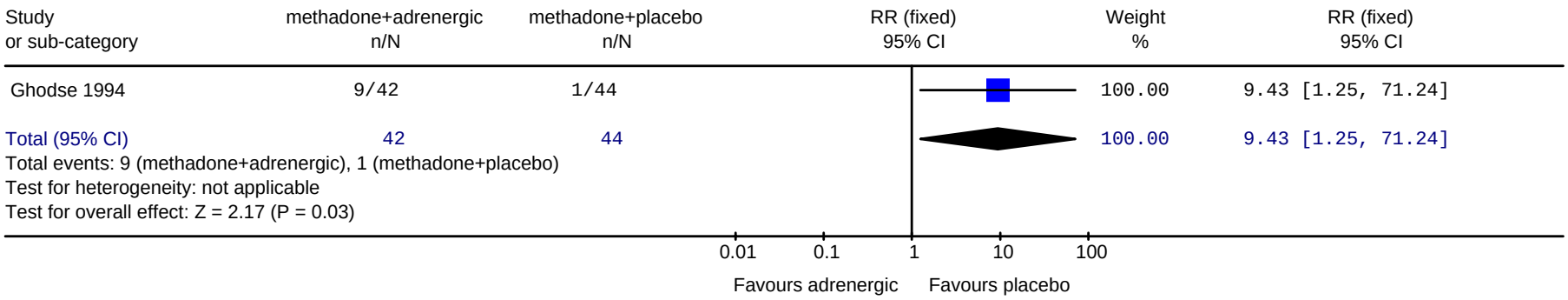
Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 03 Lofexidine versus clonidine
Outcome: 05 Adverse events: serious



Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 07 Methadone + alpha2 adrenergic agonist versus methadone + placebo
Outcome: 01 Completion of treatment

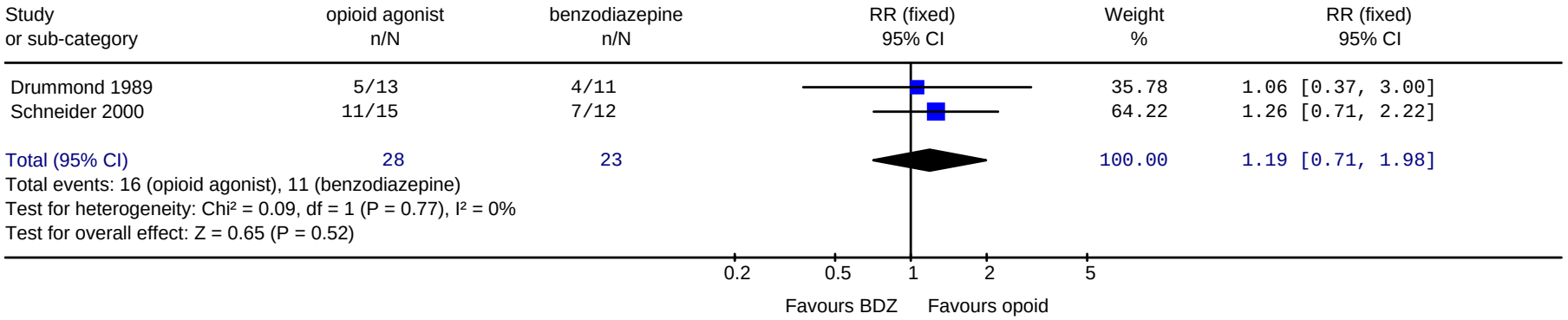


Review: DMD 3: Alpha2 adrenergic agonists
Comparison: 07 Methadone + alpha2 adrenergic agonist versus methadone + placebo
Outcome: 02 Left study early due to hypotension



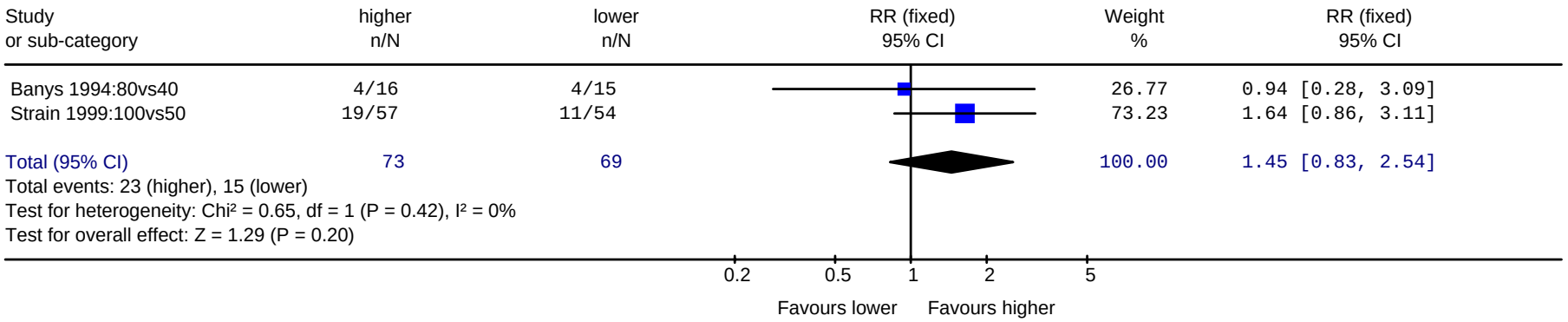
Benzodiazepines

Review: DMD 4: Benzodiazepines
Comparison: 01 Methadone/buprenorphine vs Benzodiaepines
Outcome: 01 Completion of treatment

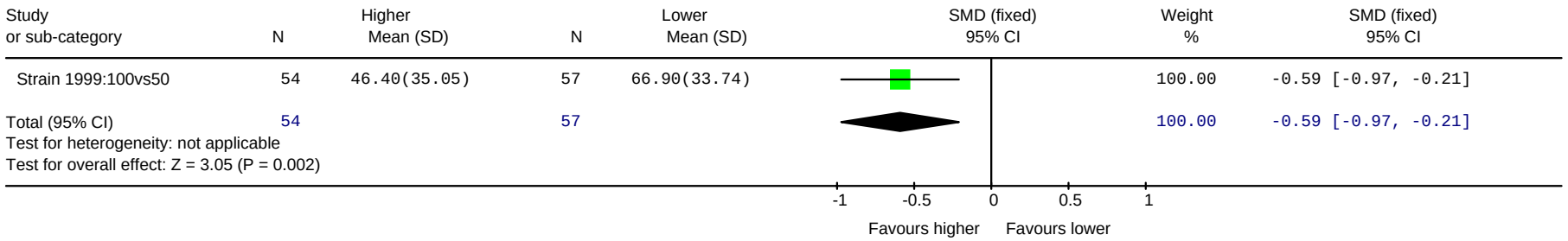


Detoxification dosage schedules

Review: DMD 5: Detoxification dosage schedules
Comparison: 02 Higher versus lower methadone starting dose
Outcome: 01 Completion of treatment

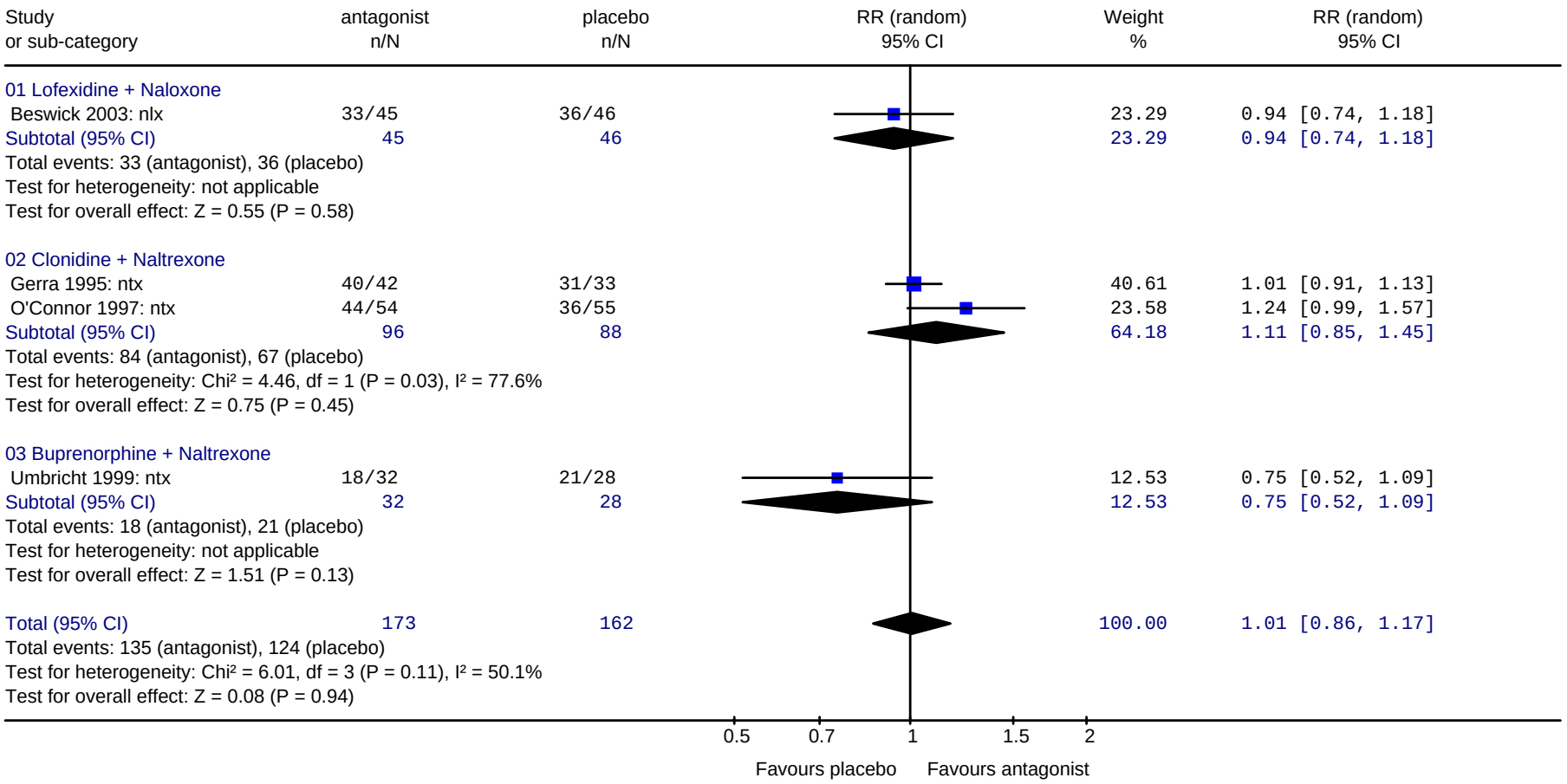


Review: DMD 5: Detoxification dosage schedules
Comparison: 02 Higher versus lower methadone starting dose
Outcome: 03 Proportion opiate-positive urines (completers analysis)

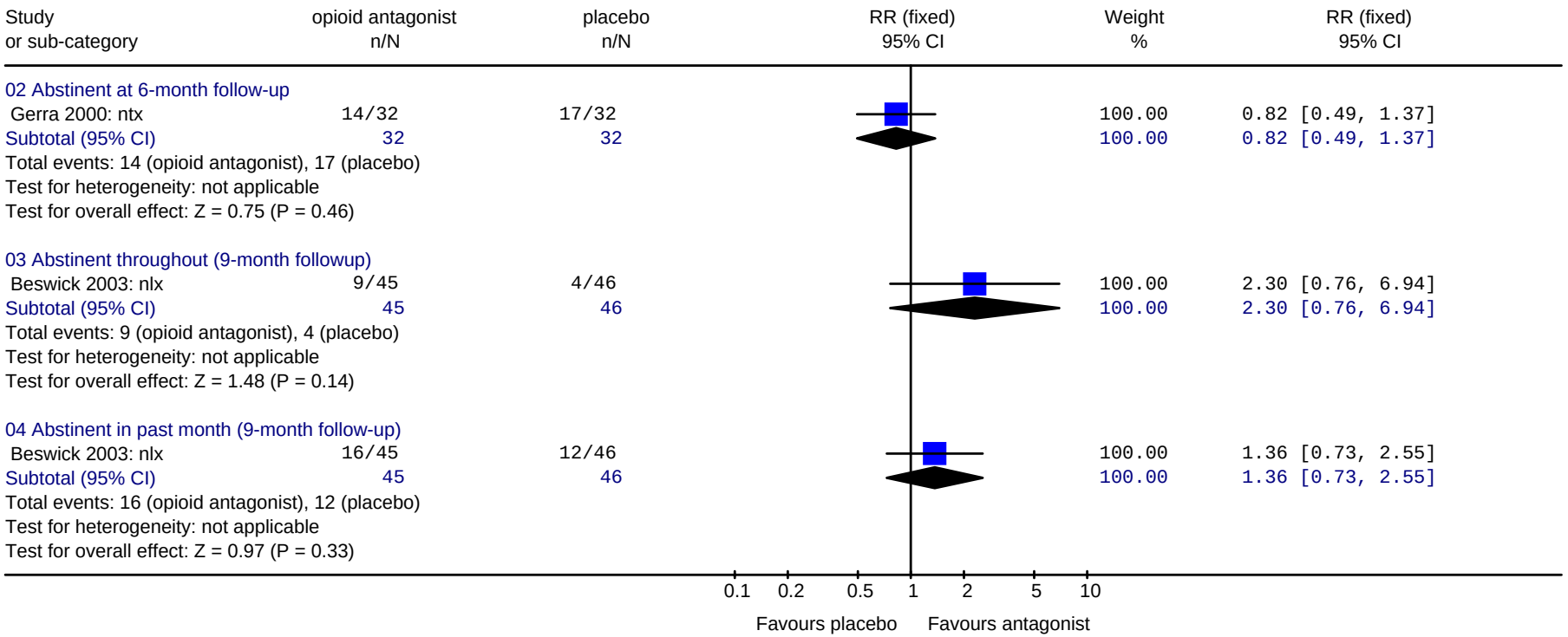


Opioid antagonist accelerated detoxification under minimal sedation

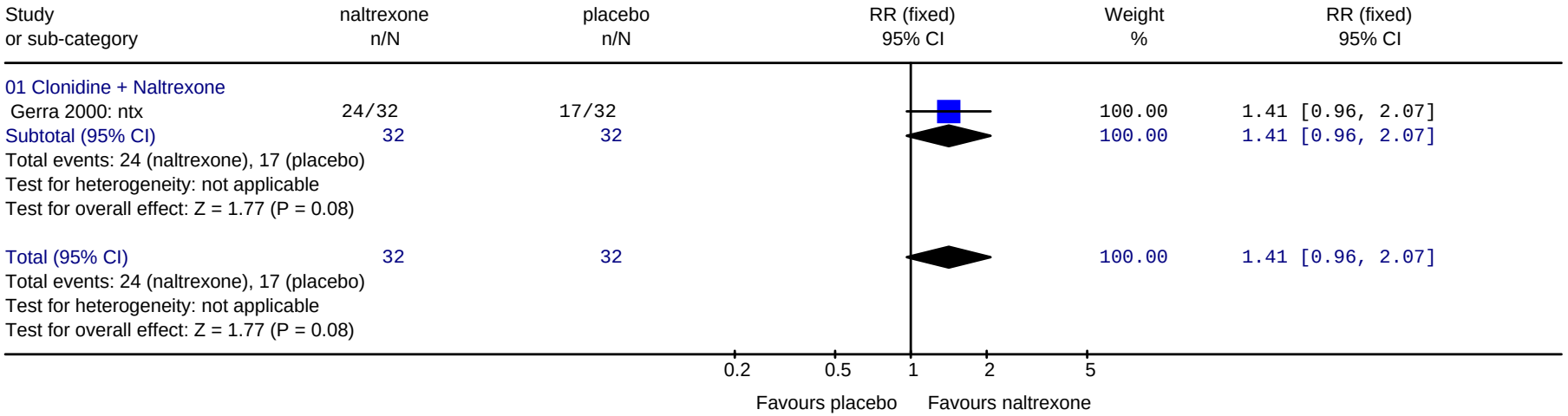
Review: DMD 6: Opioid antagonist accelerated detoxification under minimal sedation
Comparison: 06 Any pharmacological + opioid antagonist versus no opioid antagonist
Outcome: 01 Completion of treatment



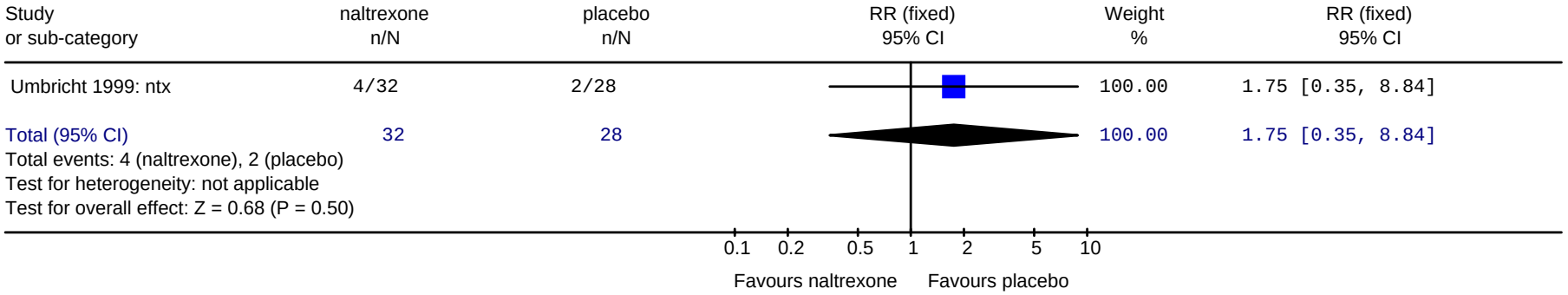
Review: DMD 6: Opioid antagonist accelerated detoxification under minimal sedation
Comparison: 06 Any pharmacological + opioid antagonist versus no opioid antagonist
Outcome: 02 Abstinence



Review: DMD 6: Opioid antagonist accelerated detoxification under minimal sedation
Comparison: 06 Any pharmacological + opioid antagonist versus no opioid antagonist
Outcome: 07 Concordance with naltrexone maintenance (3-month follow-up)

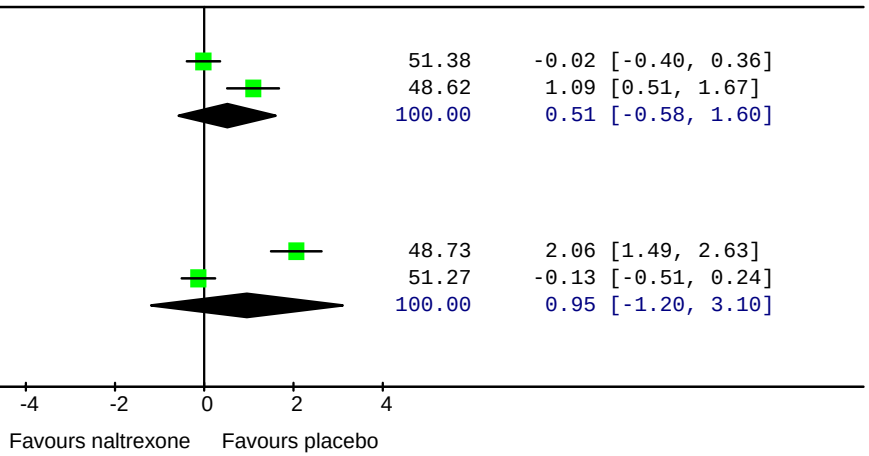


Review: DMD 6: Opioid antagonist accelerated detoxification under minimal sedation
Comparison: 06 Any pharmacological + opioid antagonist versus no opioid antagonist
Outcome: 09 Left study early due to withdrawal



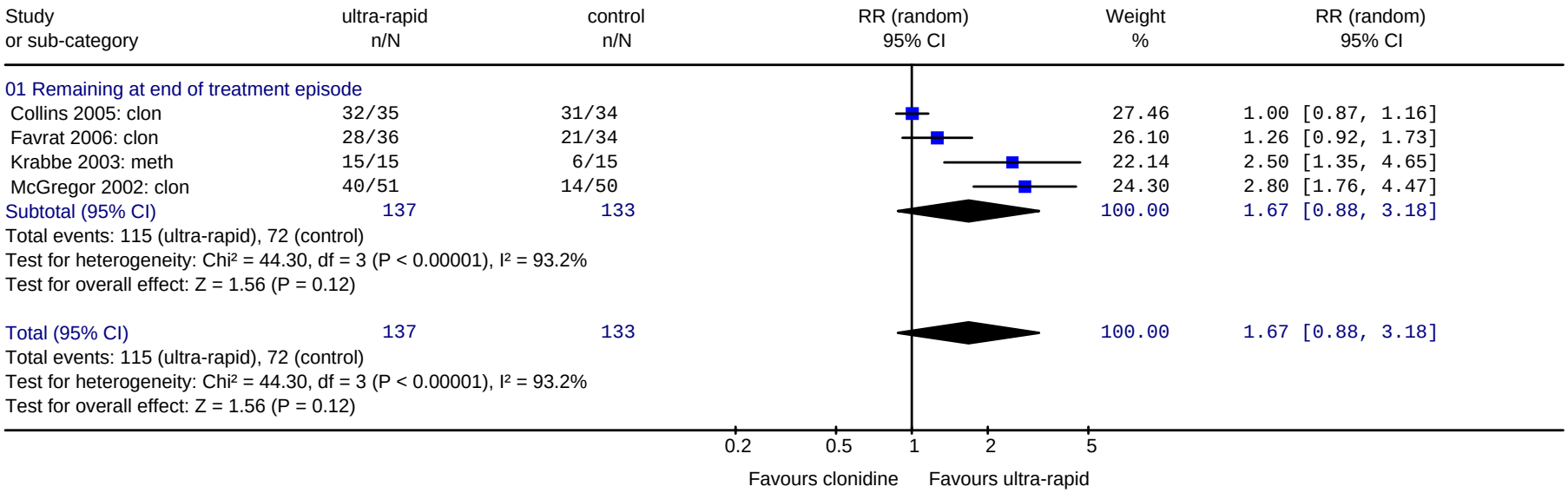
Review: DMD 6: Opioid antagonist accelerated detoxification under minimal sedation
Comparison: 06 Any pharmacological + opioid antagonist versus no opioid antagonist
Outcome: 10 Withdrawal

Study or sub-category	Naltrexone N	Naltrexone Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
03 Mean							
O'Connor 1997: ntx	54	17.60(9.30)	55	17.80(10.30)		51.38	-0.02 [-0.40, 0.36]
Umbricht 1999: ntx	25	5.20(3.30)	28	2.30(1.80)		48.62	1.09 [0.51, 1.67]
Subtotal (95% CI)	79		83			100.00	0.51 [-0.58, 1.60]
Test for heterogeneity: Chi² = 9.94, df = 1 (P = 0.002), I² = 89.9%							
Test for overall effect: Z = 0.92 (P = 0.36)							
04 Peak							
Gerra 1995: ntx	42	22.88(11.06)	33	5.44(1.87)		48.73	2.06 [1.49, 2.63]
O'Connor 1997: ntx	54	28.00(13.10)	55	29.90(14.90)		51.27	-0.13 [-0.51, 0.24]
Subtotal (95% CI)	96		88			100.00	0.95 [-1.20, 3.10]
Test for heterogeneity: Chi² = 39.86, df = 1 (P < 0.00001), I² = 97.5%							
Test for overall effect: Z = 0.87 (P = 0.39)							

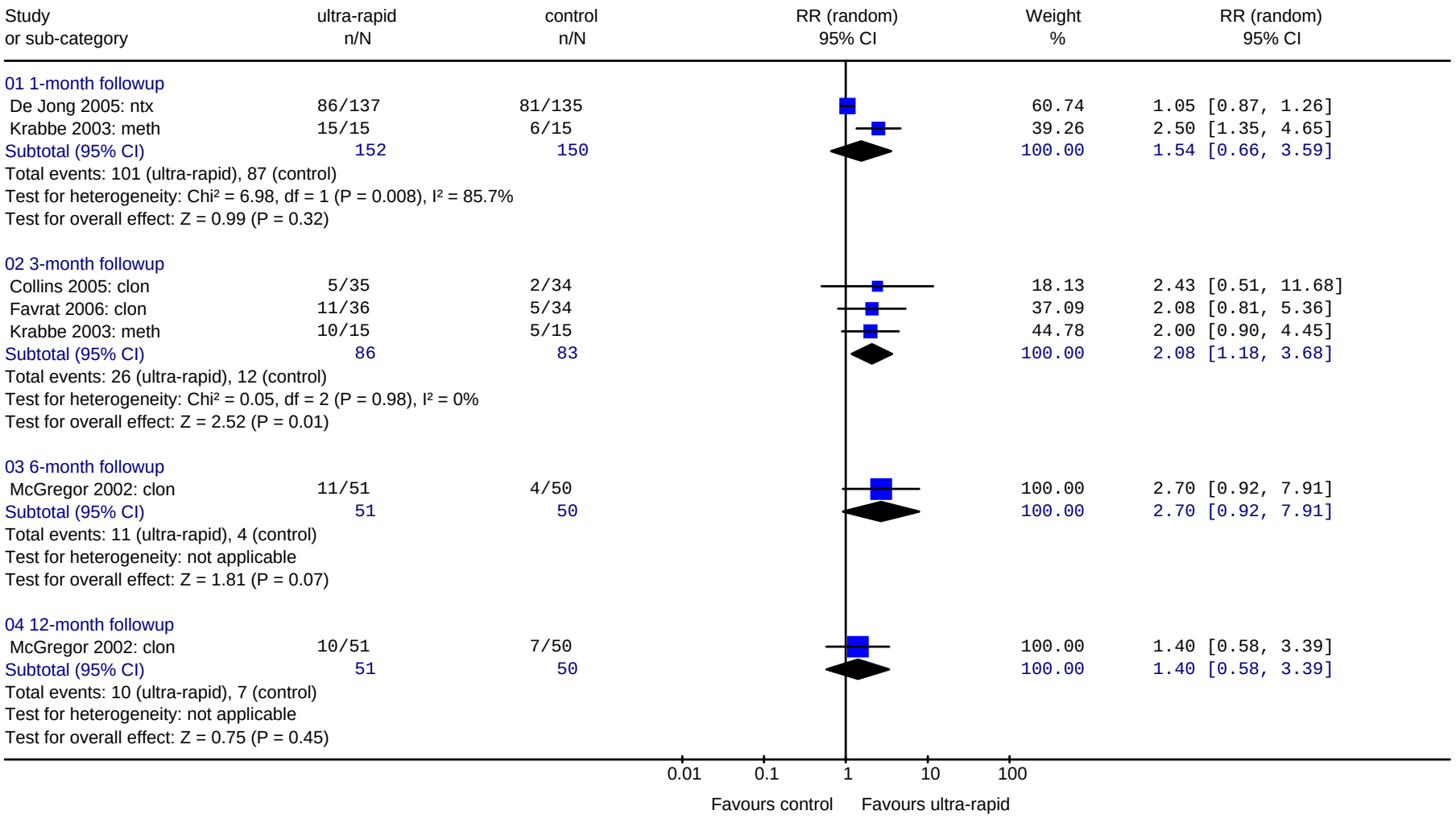


Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation

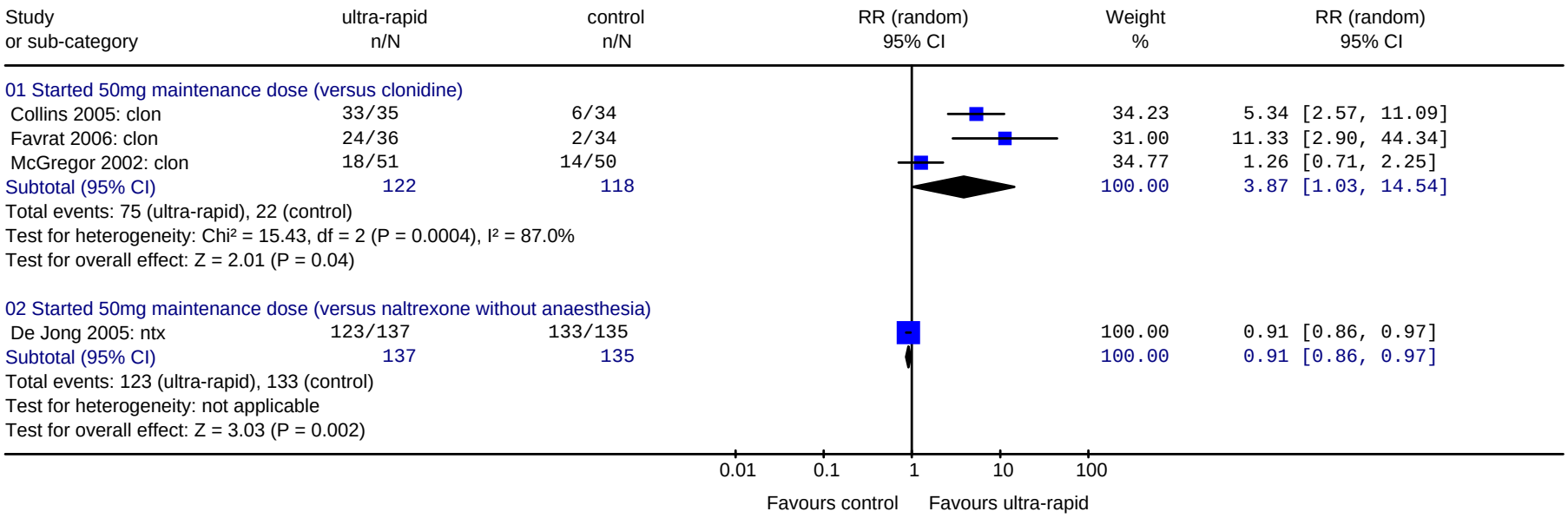
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 01 Ultra-rapid detoxification under general anaesthesia versus any pharmacological with minimal sedation
Outcome: 01 Completion of treatment



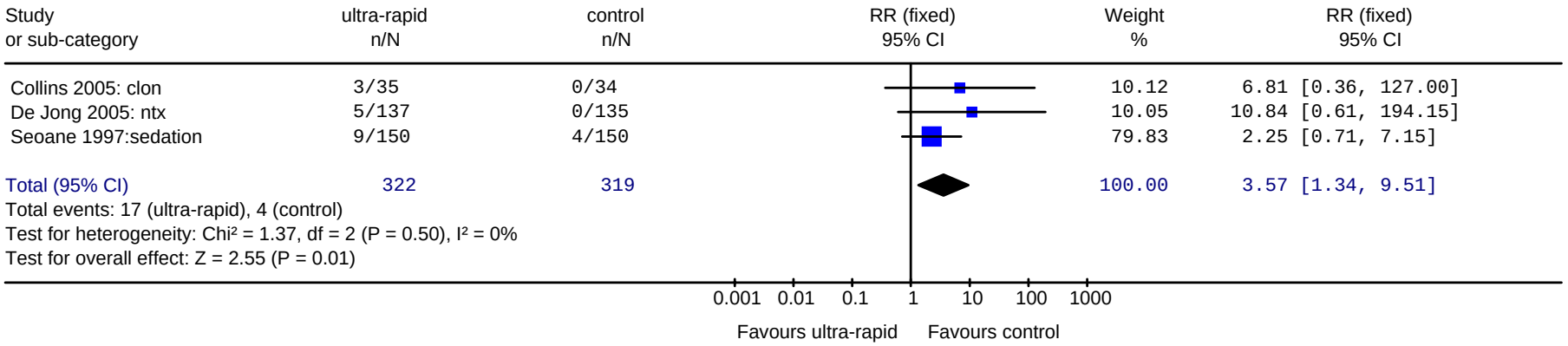
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 01 Ultra-rapid detoxification under general anaesthesia versus any pharmacological with minimal sedation
Outcome: 04 Abstinence: opiate-negative urinalysis, hair analysis or self-report



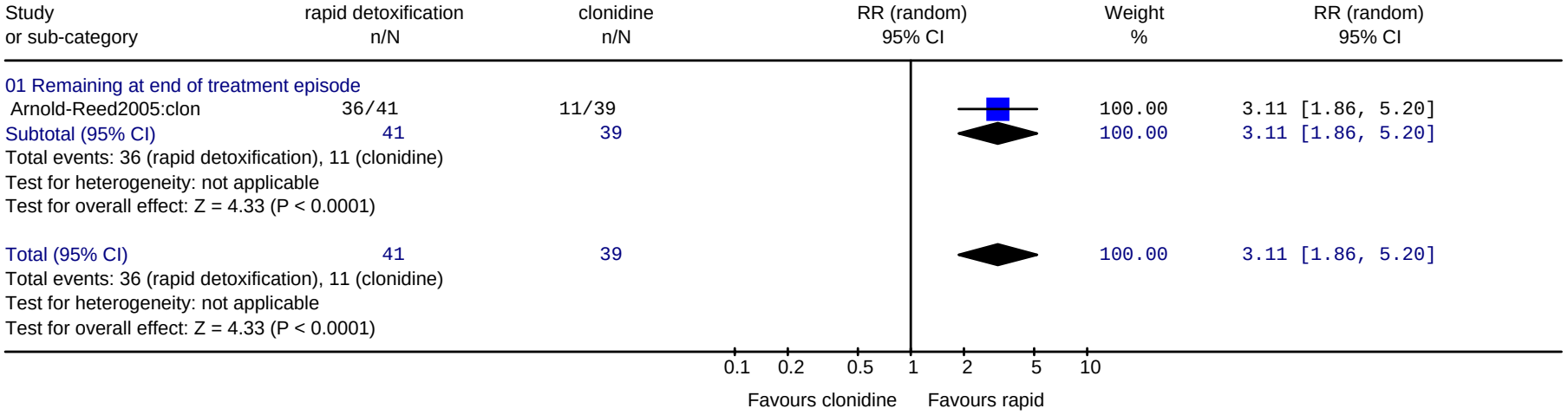
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 01 Ultra-rapid detoxification under general anaesthesia versus any pharmacological with minimal sedation
Outcome: 05 Concordance with naltrexone



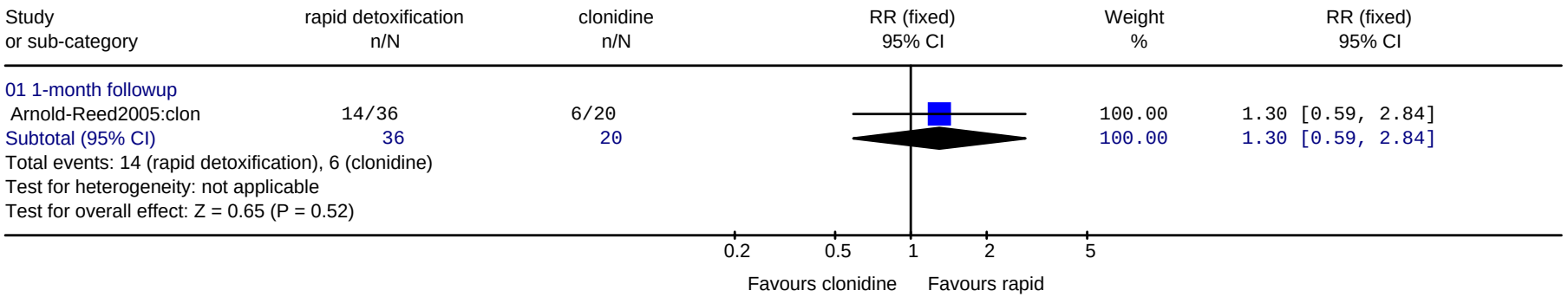
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 01 Ultra-rapid detoxification under general anaesthesia versus any pharmacological with minimal sedation
Outcome: 09 Adverse events: serious



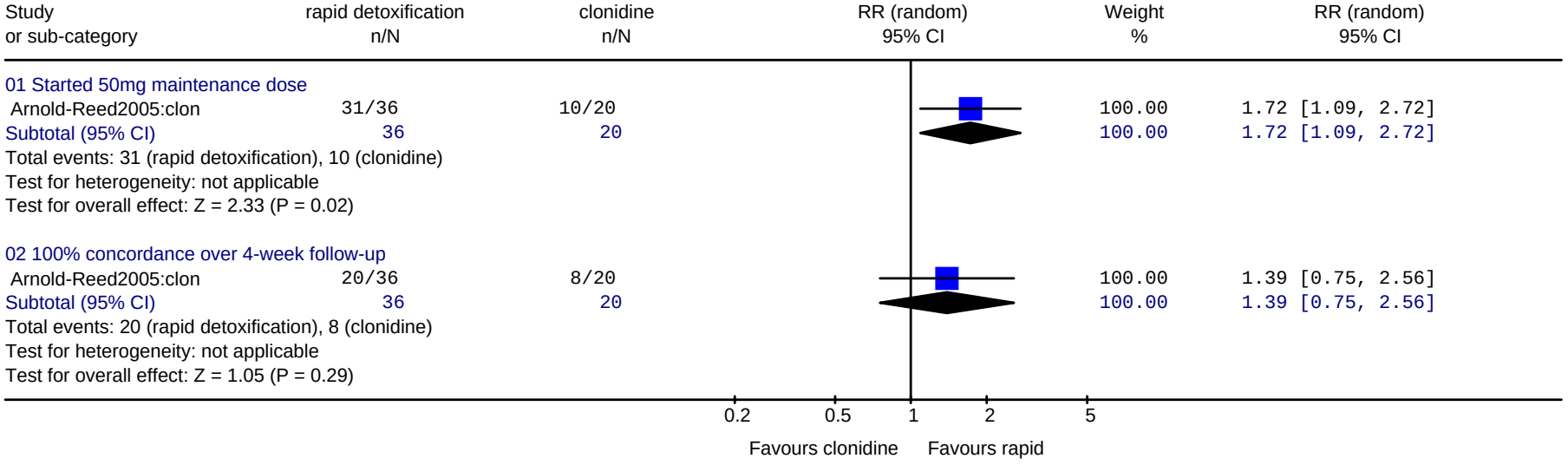
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 02 Rapid detoxification under moderate sedation versus clonidine with minimal sedation
Outcome: 01 Completion of treatment



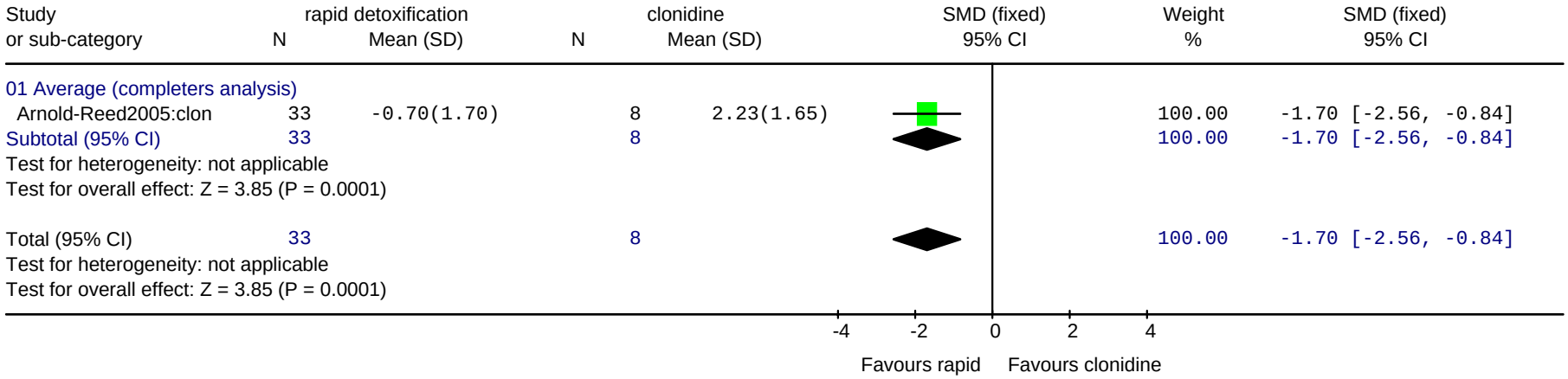
Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 02 Rapid detoxification under moderate sedation versus clonidine with minimal sedation
Outcome: 04 Abstinence: opiate-negative urinalysis, hair analysis or self-report



Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 02 Rapid detoxification under moderate sedation versus clonidine with minimal sedation
Outcome: 05 Concordance with naltrexone



Review: DMD 7: Rapid and ultra-rapid detoxification under anaesthesia or heavy sedation
Comparison: 02 Rapid detoxification under moderate sedation versus clonidine with minimal sedation
Outcome: 10 Withdrawal



Appendix 16b: Clinical evidence forest plots (psychosocial interventions in opioid detoxification)

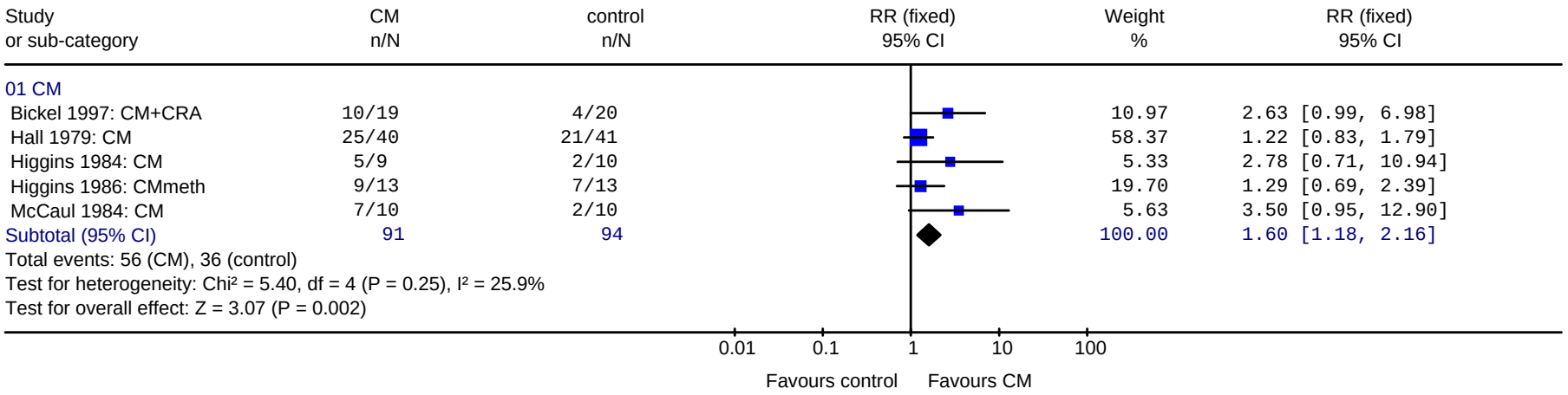
Psychosocial interventions **2**

Contingency management 2
Family interventions 5
Social network interventions 7
Individual drug counselling 8

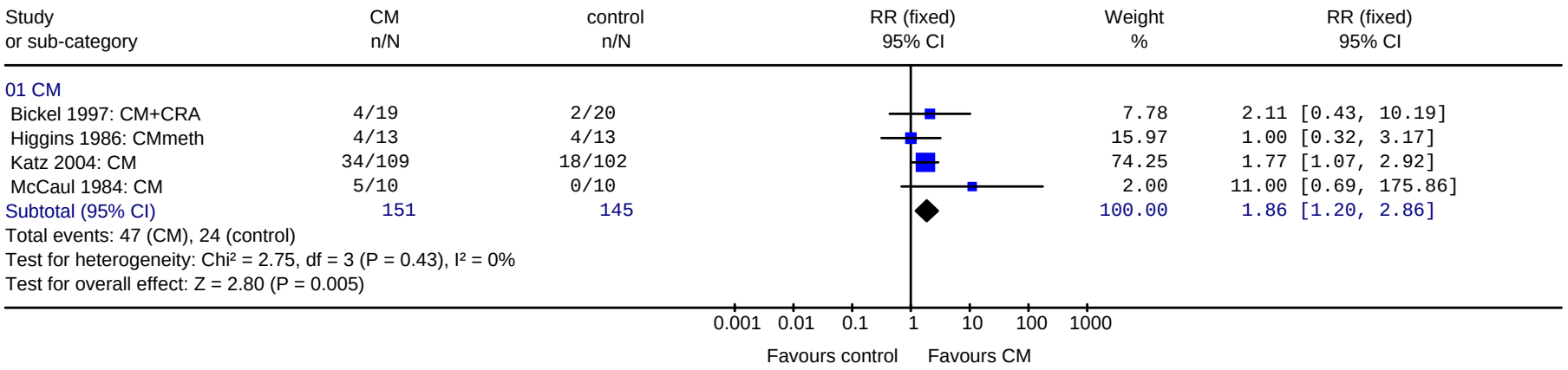
Psychosocial interventions

Contingency management

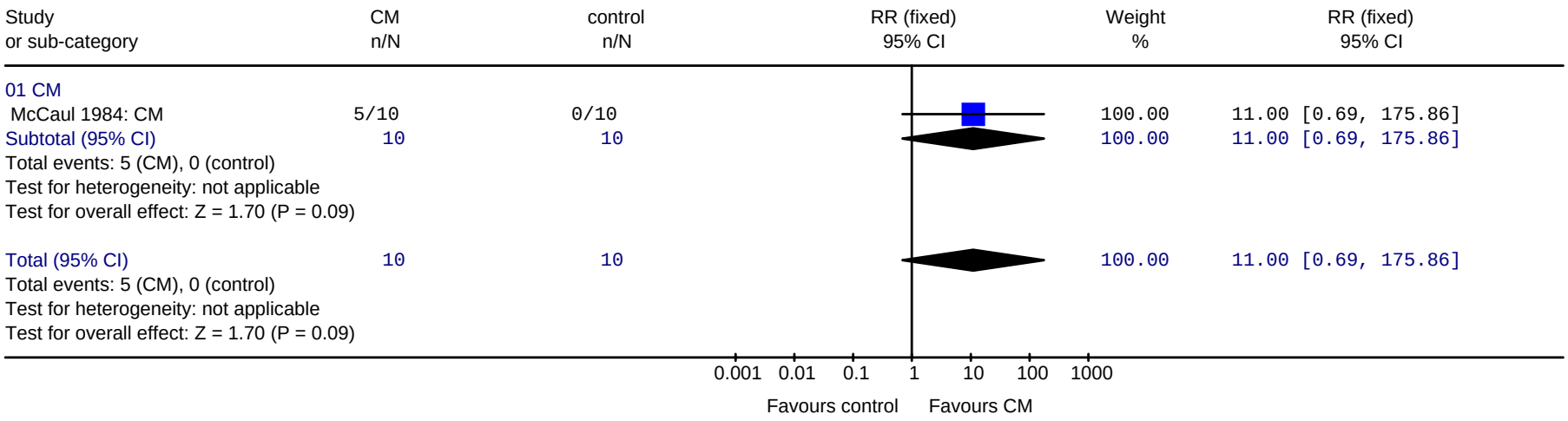
Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 02 (Detoxification + CM) versus (detoxification + control)
Outcome: 01 Completion of detoxification



Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 02 (Detoxification + CM) versus (detoxification + control)
Outcome: 02 Abstinence: opiate-negative urinalysis or self-report (endpoint)

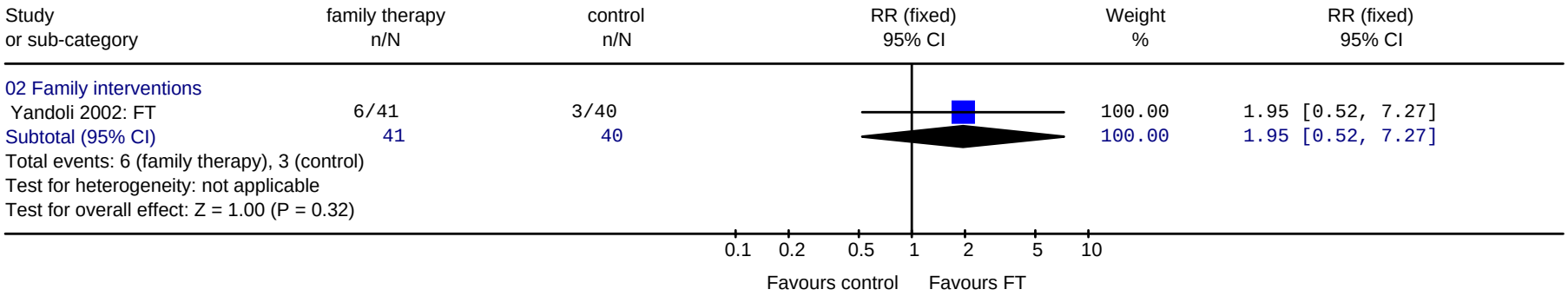


Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 02 (Detoxification + CM) versus (detoxification + control)
Outcome: 03 Abstinence: opiate-negative urinalyses for entire duration of detox

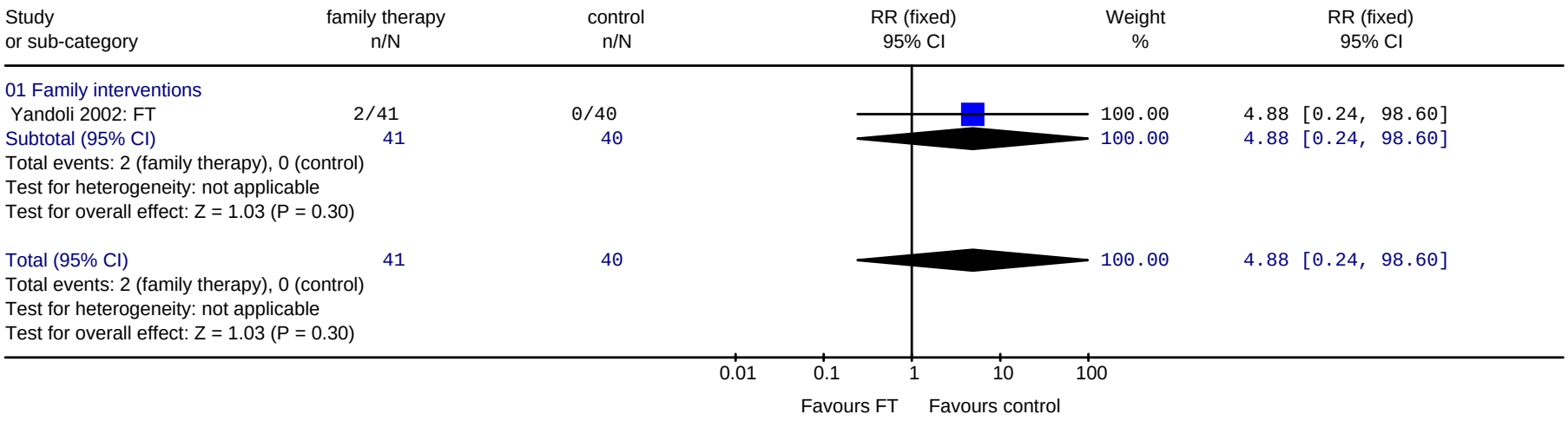


Family interventions

Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 03 (Detoxification + family interventions) versus (detoxifcation + control)
Outcome: 01 Abstinence: opiate-negative urinalysis or self-report (endpoint)

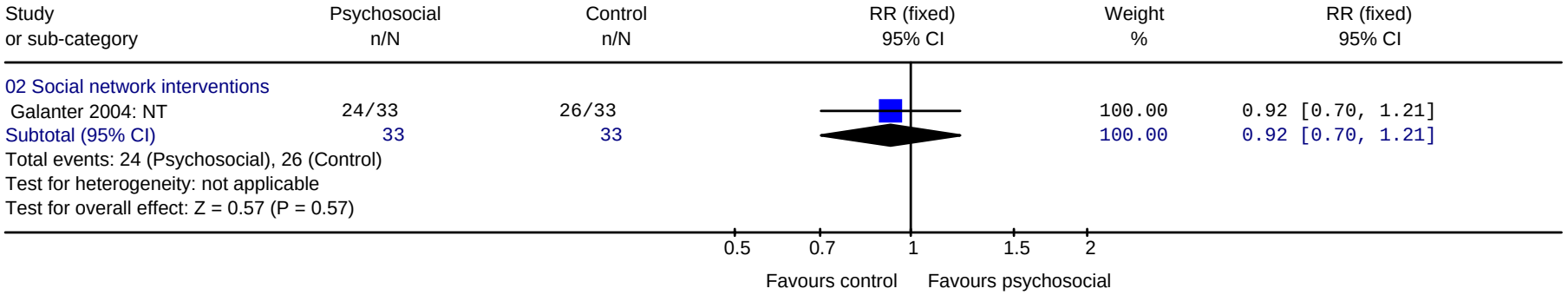


Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 03 (Detoxification + family interventions) versus (detoxifcation + control)
Outcome: 02 Mortality

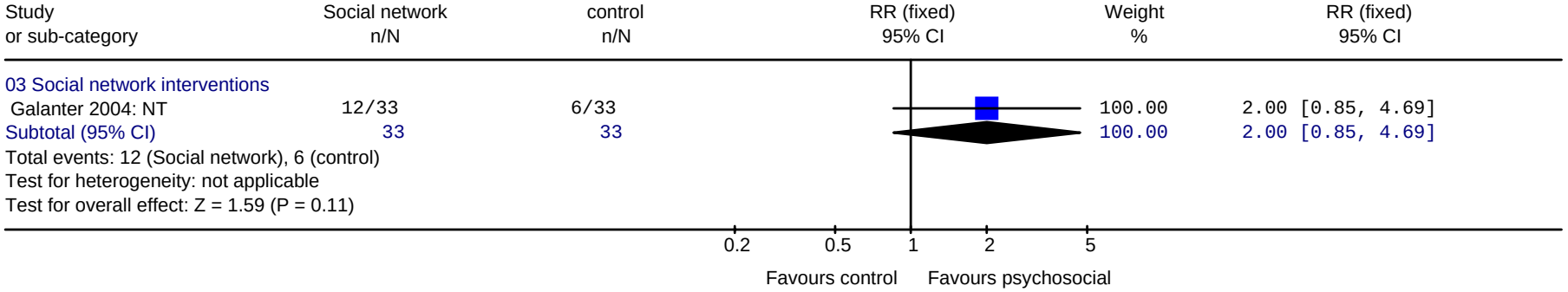


Social network interventions

Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 04 (Detoxification + social network interventions) versus (detoxification + control)
Outcome: 01 Completion of detoxification

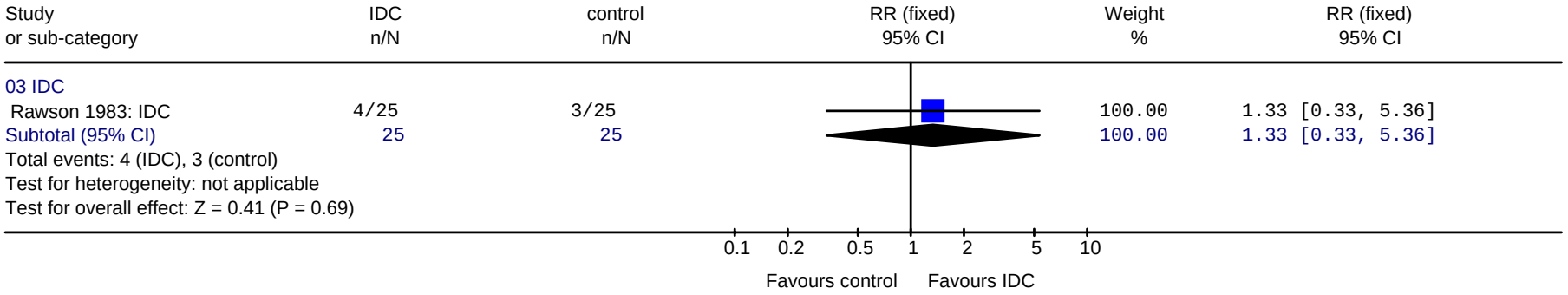


Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 04 (Detoxification + social network interventions) versus (detoxification + control)
Outcome: 02 Abstinence: opiate-negative urinalysis or self-report (endpoint)

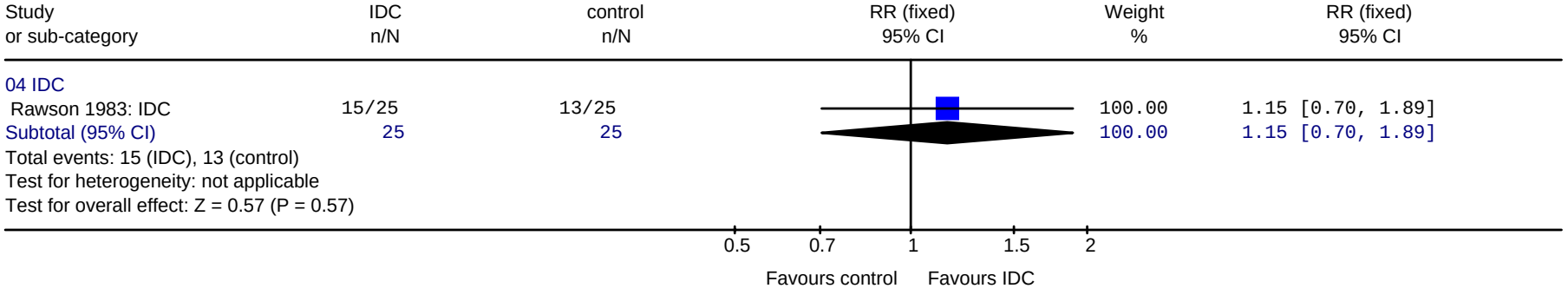


Individual drug counselling

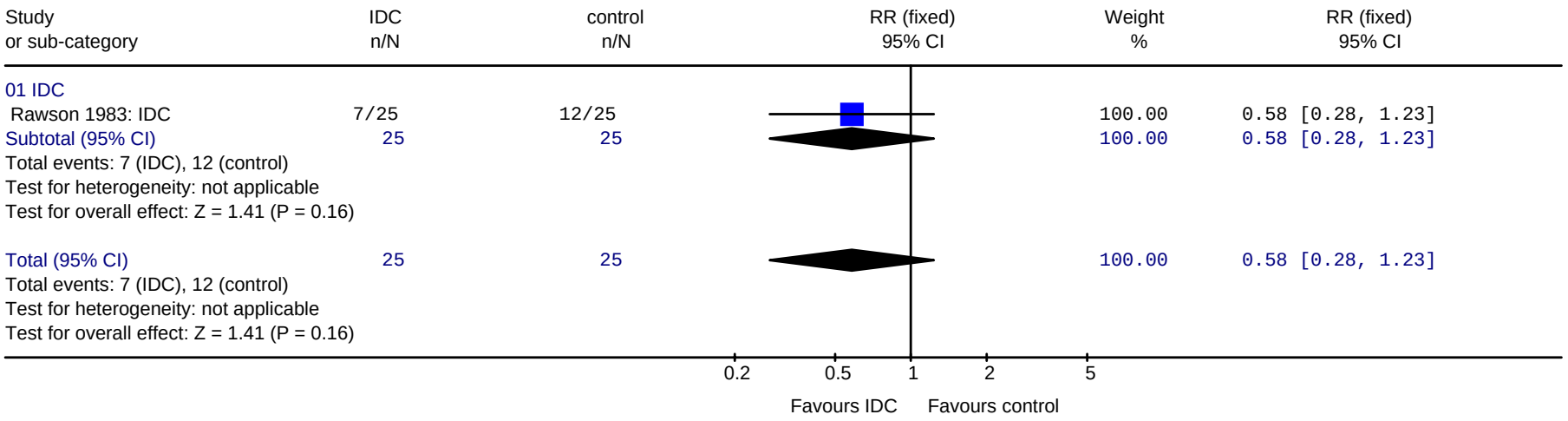
Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 05 (Detoxification + individual drug counselling) versus (detoxification + control)
Outcome: 01 Completion



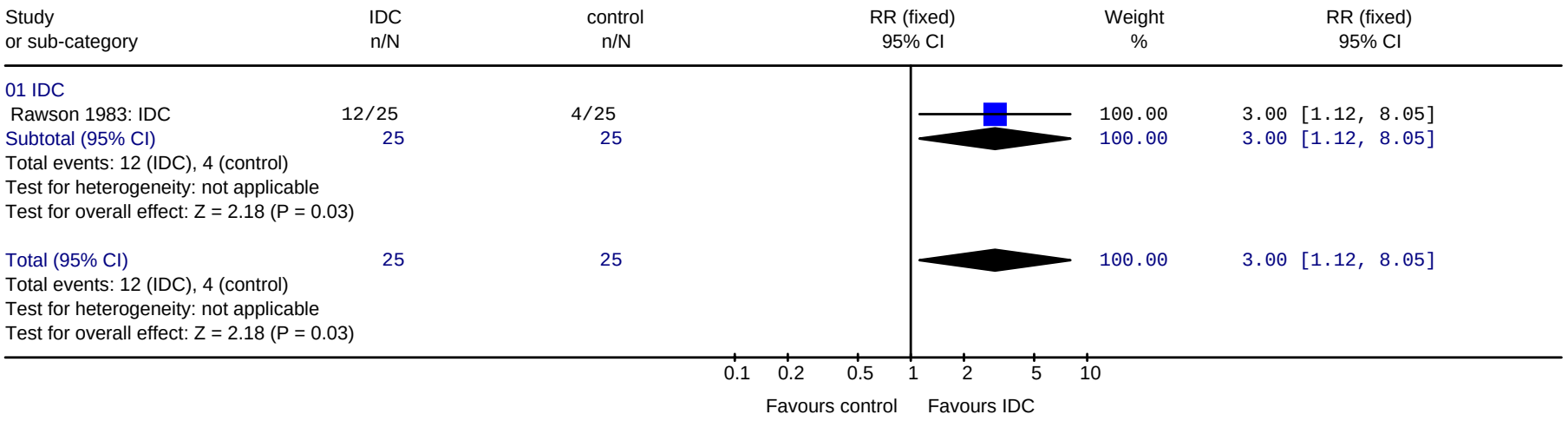
Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 05 (Detoxification + individual drug counselling) versus (detoxification + control)
Outcome: 02 Abstinence: opiate-negative urinalysis or self-report (endpoint)



Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 05 (Detoxification + individual drug counselling) versus (detoxification + control)
Outcome: 03 Relapse: drug dependent or incarcerated (6-month followup)



Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 05 (Detoxification + individual drug counselling) versus (detoxification + control)
Outcome: 04 Engagement in long-term treatment (endpoint)



Appendix 16c: Clinical evidence forest plots (treatment settings for opioid detoxification)

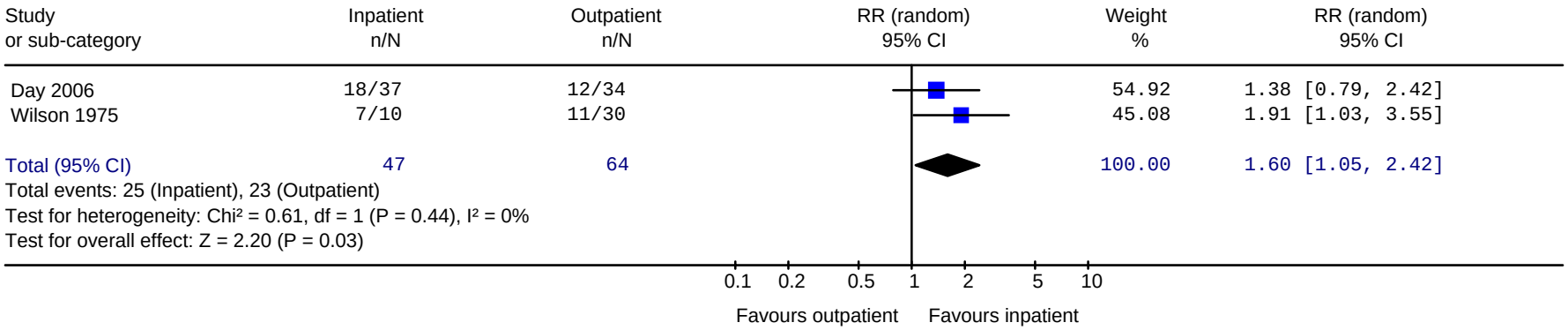
Settings **2**

Inpatient settings 2

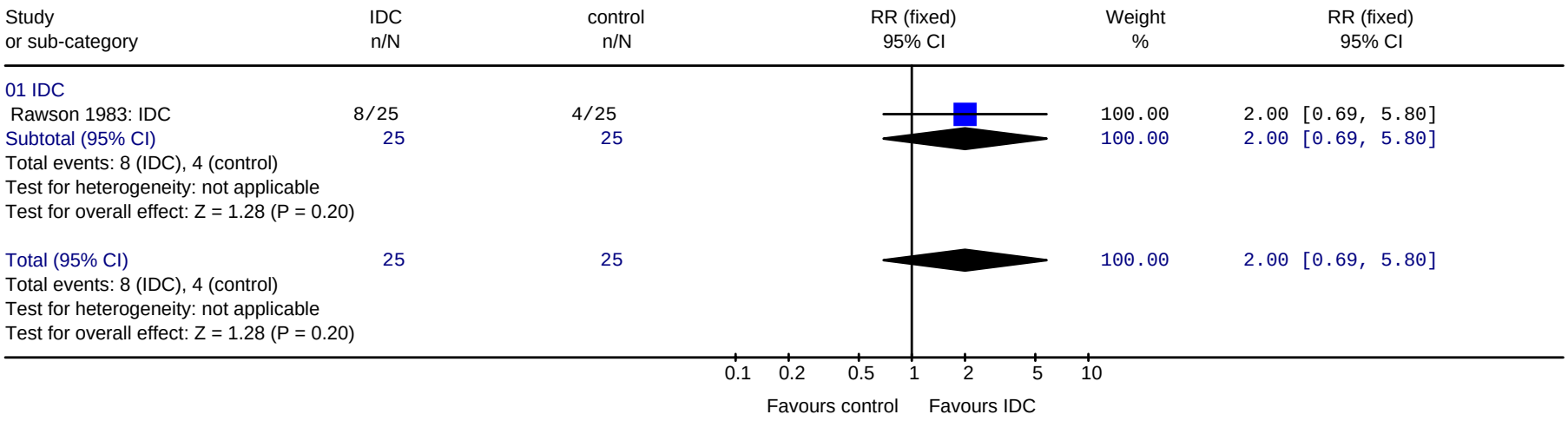
Settings

Inpatient settings

Review: DMD: Settings
Comparison: 01 Inpatient vs Outpatient
Outcome: 01 Completion



Review: DMD 8: Detoxification + psychosocial intervention
Comparison: 05 (Detoxification + individual drug counselling) versus (detoxification + control)
Outcome: 05 Engagement in long-term treatment (6-month followup)



Appendix 17a: Evidence profile tables A17-1 to A17-14 (pharmacological interventions in opioid detoxification)

Pharmacological interventions **2**

Table A17-1. Methadone versus clonidine 2
Table A17-2. Methadone versus other opioid agonists (not buprenorphine) 5
Table A17-3. Methadone versus lofexidine 7
Table A17-4. Buprenorphine versus clonidine 9
Table A17-5. Buprenorphine versus lofexidine 11
Table A17-6. Buprenorphine versus methadone 13
Table A17-7. Buprenorphine versus dihydrocodeine 15
Table A17-8. Lofexidine versus clonidine 17
Table A17-9. Methadone plus adrenergic agonist versus methadone plus placebo 19
Table A17-10. Opioid agonist versus benzodiazepine 20
Table A17-11. Higher versus lower methadone dose 21
Table A17-12. Opioid antagonist-accelerated detoxification versus no opioid antagonist 22
Table A17-13. Ultra-rapid detoxification under general anaesthesia or heavy sedation versus detoxification under minimal sedation 25
Table A17-14. Rapid detoxification under moderate sedation versus clonidine 28

Pharmacological interventions

Table A17-1. Methadone versus clonidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Kleber1985, San1990, Umbricht2003, Washton1980)					
4	Randomised trials	No limitations	No important inconsistency	No uncertainty	None
Started naltrexone maintenance (Gerra2000)					
1	Randomised trials	Serious limitations (-1)[4]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]
Abstinence during treatment (Kleber1985)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]
Abstinence at endpoint (Kleber1985, Washton1980)					
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2]
Abstinence at 1-month follow-up (Kleber1985)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,3]
Abstinence at 3-month follow-up (Kleber1985)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,3]
Abstinence at 6-month follow-up (Kleber1985)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,3]
Self-rated withdrawal severity: peak (Kleber1985. Better indicated by: lower scores)					

1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]
Self-rated withdrawal severity: mean change from baseline (Umbricht2003. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,3]
Adverse events: side effects rating (Kleber1985, Washton1982. Better indicated by: lower scores)					
2	Randomised trials	Serious limitations (-1)[4]	No important inconsistency	No uncertainty	Very strong association (+2)[5]

Summary of findings

Outcome	No of patients		Effect		Quality
	Methadone	Clonidine	Relative (95% CI)	Absolute (95% CI)	
Completion of Treatment	57/99 (57.6%)	80/188 (42.6%)	RR 1.5 (1.19 to 1.9)	-	⨁⨁⨁⨁ High
Entry into naltrexone maintenance (methadone vs clonidine)	9/34 (26.5%)	17/32 (53.1%)	RR 0.50 (0.26 to 0.95)	-	⨁⨁◯◯ Low
Abstinence during treatment	13/25 (52%)	10/24 (41.7%)	RR 1.25 (0.68 to 2.29)	-	⨁⨁⨁◯ Moderate
Abstinence at endpoint	15/38 (39.5%)	14/37 (37.8%)	RR 1.04 (0.58 to 1.85)	-	⨁⨁⨁◯ Moderate
Abstinence at 1-month follow-up	8/25 (32%)	6/24 (25%)	RR 1.28 (0.52 to 3.14)	-	⨁⨁⨁◯ Moderate
Abstinence at 3-month follow-up	8/25 (32%)	6/24 (25%)	RR 1.28 (0.52 to 3.14)	-	⨁⨁⨁◯ Moderate

Abstinence at 6-month follow-up	9/25 (36%)	4/24 (16.7%)	RR 2.16 (0.77 to 6.09)	-	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: peak	25	25	-	SMD -0.65 (-1.22 to -0.08)	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: Mean change from baseline	18	18	-	SMD 0.25 (-0.4 to 0.91)	⨁⨁⨁◯ Moderate
Adverse events: Side effects rating	125	125	-	SMD -0.92 (-1.18 to -0.66)	⨁⨁⨁⨁ High

Footnotes:

1. Significant heterogeneity (I^2 >= 50%)
2. CIs do not favour either treatment
3. Single study
4. No blinding
5. Large effect (SMD <= -0.8)

Table A17-2. Methadone versus other opioid agonists (not buprenorphine)

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of Treatment (Salehi2006, Sorensen1982, Tennant1975, Tennant1978)					
4	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	Imprecise or sparse data (-1)[3]
Abstinence at endpoint (Tennant1975)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[2]	Imprecise or sparse data (-1)[3,4]
Abstinence at 1-month follow-up (Tennant1975, Tennant1978)					
2	Randomised trials	No limitations	Important inconsistency (-1)[1]	Some uncertainty (-1)[2]	Imprecise or sparse data (-1)[3,4]
Abstinence at 6-month follow-up (Tennant1978)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[2]	Imprecise or sparse data (-1)[3,4]

Summary of findings

Outcome	No of patients		Effect		Quality
	Methadone	Any Other Pharmacological Intervention	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	66/99 (66.7%)	96/188 (51.1%)	RR 1.20 (0.7 to 2.07)	-	⨁⨁◯◯ Low
Abstinence at endpoint	10/36 (27.8%)	11/36 (30.6%)	RR 0.91 (0.44 to 1.87)	-	⨁⨁◯◯ Low

Abstinence at 1-month follow-up	5/44 (11.4%)	7/42 (16.7%)	RR 0.54 (0.02 to 14.86)	-	⊕◯◯◯ Very low
Abstinence at 6-month follow-up	1/12 (8.3%)	2/10 (20%)	RR 0.42 (0.04 to 3.95)	-	⊕⊕◯◯ Low

Footnotes:

1. Significant heterogeneity (I^2 > 50%)
2. Old studies
3. CIs do not favour either treatment
4. Single study

Table A17-3. Methadone versus lofexidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion (Bearn1996, Howells2002)					
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	None
Self-rated withdrawal severity: Peak (Howells2002. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2]
Self-rated withdrawal severity: Lowest (Howells2002. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2]
Self-rated withdrawal severity: Total or mean (Howells2002. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2]
Adverse events: Hypotension (Howells2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2]

Summary of findings

Outcome	No of patients		Effect		Quality
	Methadone	Lofexidine	Relative (95% CI)	Absolute (95% CI)	
Completion	62/80 (77.5%)	47/74 (63.5%)	RR 1.22 (0.99 to 1.51)	-	⨁⨁⨁⨁ High
Self-rated withdrawal severity: Peak	34	29	-	SMD -0.09 (-0.58 to 0.41)	⨁⨁⨁◯ Moderate

Self-rated withdrawal severity: Lowest	34	29	-	SMD -0.03 (-0.53 to 0.47)	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: Total or mean	34	29	-	SMD -0.12 (-0.62 to 0.37)	⨁⨁⨁◯ Moderate
Adverse events: Hypotension	3/36 (8.3%)	4/32 (12.5%)	RR 0.67 (0.16 to 2.76)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. Single study
2. CIs do not favour either treatment

Table A17-4. Buprenorphine versus clonidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Cheskin1994, Janiri1994, Lintzeris2002, Marsch2005, Nigam1993, O'Connor1997, Umbricht2003)					
7	Randomised trials	No limitations	No important inconsistency	No uncertainty	None
Started naltrexone maintenance (Marsch2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1] Very strong association (+2)[2]
Abstinence during treatment (Lintzeris2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[3]
Abstinence at endpoint (Ling2005: inpatient, Ling2005: outpatient, Lintzeris2002)					
3	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[3]
Abstinence maintained for 4 weeks post-treatment (Lintzeris2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[4] Strong association (+1)[3]
Left study early due to adverse events (Cheskin1994, Nigam1993, Umbricht2003)					
3	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[4] Very strong association (+2)[2]
Drug use: days during 4-week follow-up (Lintzeris2002. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[5]

Summary of findings

Outcome	No of patients		Effect		Quality
	Buprenorphine	Clonidine	Relative (95% CI)	Absolute (95% CI)	
Completion	156/211 (73.9%)	121/216 (56%)	RR 1.32 (1.15 to 1.52)	-	⊕⊕⊕⊕ High
Initiated naltrexone maintenance	11/18 (61.1%)	1/18 (5.6%)	RR 11.00 (1.58 to 76.55)	-	⊕⊕⊕⊕ High
Abstinence during treatment	13/58 (22.4%)	3/56 (5.4%)	RR 4.18 (1.26 to 13.90)	-	⊕⊕⊕⊕ High
Abstinence at endpoint	117/292 (40.1%)	14/166 (8.4%)	RR 4.29 (2.60 to 7.09)	-	⊕⊕⊕⊕ High
Abstinence maintained for 4 weeks post-treatment	5/58 (8.6%)	1/56 (1.8%)	RR 4.83 (0.58 to 40.03)	-	⊕⊕⊕⊕ High
Left study early due to adverse events	0/55 (0%)	6/51 (11.8%)	RR 0.19 (0.03 to 1.03)	-	⊕⊕⊕⊕ High
Drug use: days during 28 days follow-up	48	43	-	SMD -0.61 (-1.03 to -0.19)	⊕⊕⊕⊕ High

Footnotes:

1. Single study
2. Very large effect (RR >= 5 or <= 0.2)
3. Large effect (RR >=2 or <= 0.5)
4. CIs do not favour either treatment
5. Large effect (SMD <= -0.5)

Table A17-5. Buprenorphine versus lofexidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion (Raistrick2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	None
Abstinence at 1-month follow-up (Raistrick2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Self-rated withdrawal severity: Peak (Raistrick 2005. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Self-rated withdrawal severity: Lowest (Raistrick 2005. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	None
Self-rated withdrawal severity: Mean (Raistrick 2005. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[2]
Self-rated withdrawal: Mean change from baseline (Raistrick2005. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Buprenorphine	Lofexidine	Relative (95% CI)	Absolute (95% CI)	
Completion	70/107 (65.4%)	47/103 (45.6%)	RR 1.43 (1.11 to 1.84)	-	⨁⨁⨁⨁ High

Abstinence at 1-month follow-up	37/107 (34.6%)	26/103 (25.2%)	RR 1.37 (0.90 to 2.09)	-	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: Peak	106	102	-	SMD -0.18 (-0.45 to 0.1)	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: Lowest	106	102	-	SMD -0.46 (-0.74 to -0.19)	⨁⨁⨁⨁ High
Self-rated withdrawal severity: Mean	106	102	-	SMD -0.50 (-0.78 to -0.22)	⨁⨁⨁⨁ High
Self-rated withdrawal: Mean change from baseline	105	102	-	SMD -0.11 (-0.38 to 0.17)	⨁⨁⨁◯ Moderate

Footnotes:

1. CIs do not favour either treatment
2. Large effect (SMD <= -0.5)

Table A17-6. Buprenorphine versus methadone

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion (Johnson1992, Petitjean2002, Seifert2002, Umbricht2003)					
4	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Relapse to opiate use during treatment (Seifert2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2,3]
Self-rated withdrawal severity: Mean change from baseline (Umbricht2003. Better indicated by: lower scores)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,2,3]

Summary of findings

Outcome	No of patients		Effect		Quality
	Buprenorphine	Methadone	Relative (95% CI)	Absolute (95% CI)	
Completion	47/107 (43.9%)	41/105 (39%)	RR 1.10 (0.82 to 1.48)	-	⨁⨁⨁◯ Moderate
Relapse to opiate use during treatment	1/14 (7.1%)	2/12 (16.7%)	RR 0.43 (0.04 to 4.16)	-	⨁⨁⨁◯ Moderate
Self-rated withdrawal severity: Mean change from baseline	21	18	-	SMD -0.44 (-1.08 to 0.20)	⨁⨁⨁◯ Moderate

Footnotes:

1. CIs do not favour either treatment
2. Small N
3. Single study

Table A17-7. Buprenorphine versus dihydrocodeine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion (Wright2007a, Wright2007b)					
2	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	None
Abstinence at endpoint (Wright 2007a, 2007b)					
2	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	None
Abstinence at 1-month follow-up (Wright 2007b)					
1	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Abstinence at 3-month follow-up (Wright 2007a,b)					
2	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Abstinence at 6-month follow-up (Wright 2007a, b)					
2	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Buprenorphine	Dihydrocodeine	Relative (95% CI)	Absolute (95% CI)	
Completion	41/70 (58.6%)	37/80 (46.2%)	RR 1.27 (0.97 to 1.66)	-	⨁⨁⨁◯ Moderate

Abstinence at endpoint	30/70 (42.9%)	18/80 (22.5%)	RR 1.90 (1.21 to 3.01)	-	⨁⨁⨁◯ Moderate
Abstinence at 1-month follow-up	16/42 (38.1%)	17/48 (35.4%)	RR 1.08 (0.63 to 1.85)	-	⨁⨁◯◯ Low
Abstinence at 3-month follow-up	23/70 (32.9%)	16/80 (20%)	RR 1.64 (0.94 to 2.86)	-	⨁⨁◯◯ Low
Abstinence at 6-month follow-up	12/70 (17.1%)	8/80 (10%)	RR 1.71 (0.74 to 3.96)	-	⨁⨁◯◯ Low

Footnotes:

1. CIs do not favour either intervention
2. No blinding

Table A17-8. Lofexidine versus clonidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Carnwath1998, Gerra2001)					
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1,]
Abstinence at 1-month follow-up (Carnwath1998)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Initiation of naltrexone maintenance (Gerra2001)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Adverse events: Hypotension (Kahn1997, Lin1997)					
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3]
Serious adverse events (Kahn1997)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,3] Very strong association (+2)[4]

Summary of findings

Outcome	No of patients		Effect		Quality
	Lofexidine	Clonidine	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	35/46 (76.1%)	29/44 (65.9%)	RR 1.16 (0.90 to 1.50)	-	⨁⨁⨁◯ Moderate
Abstinence at 1-month follow-up	17/26 (65.4%)	12/24 (50%)	RR 1.31 (0.80 to 2.13)	-	⨁⨁⨁◯ Moderate

Initiation of naltrexone maintenance	14/20 (70%)	13/20 (65%)	RR 1.08 (0.77 to 1.66)	-	⨁⨁⨁◯ Moderate
Adverse events: Hypotension	21/54 (38.9%)	29/54 (53.7%)	RR 0.72 (0.48 to 1.08)	-	⨁⨁⨁◯ Moderate
Serious adverse events	0/14 (0%)	4/14 (28.6%)	RR 0.11 (0.01 to 1.89)	-	⨁⨁⨁⨁ High

Footnotes:

1. Small N
2. Single study
3. CIs do not favour either intervention
4. Very large effect (RR <= 0.2 or >= 5)

Table A17-9. Methadone plus adrenergic agonist versus methadone plus placebo

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Ghodse1994, San1994)					
2	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	None
Left study early due to hypertension (Ghodse1994)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2] Very strong association (+2)[3]

Summary of findings

Outcome	No of patients		Effect		Quality
	Methadone + adrenergic agonist	Methadone alone	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	58/111 (52.3%)	63/119 (52.9%)	RR 0.98 (0.77 to 1.25)	/1 000 (to)	⨁⨁⨁◯ Moderate
Left study early due to hypertension	9/42 (21.4%)	1/44 (2.3%)	RR 9.43 (1.25 to 71.24)	/1 000 (to)	⨁⨁⨁⨁ High

Footnotes:

1. Significant heterogeneity (I^2 >= 0.5)
2. Single study
3. Very large effect (RR >= 5 or <= 0.2)

Table A17-10. Opioid agonist versus benzodiazepine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Drummond1989, Schneider2000)					
2	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Methadone or buprenorphine	Benzodiazepines	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	16/28 (57.1%)	11/23 (47.8%)	RR 1.19 (0.71 to 1.98)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. CIs do not favour either treatment

Table A17-11. Higher versus lower methadone dose

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Banys 1994, Strain 1999)					
0	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Higher methdone dose	Lower methadone dose	Relative (95% CI)	Absolute (95% CI)	
Completion of detoxification	23/73 (31.5%)	15/69 (21.7%)	RR 1.45 (0.83 to 2.54)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. CIs do not favour either treatment

Table A17-12. Opioid antagonist-accelerated detoxification versus no opioid antagonist

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Beswick2003, Gerra1995, O'Connor1997, Umbricht1999)					
4	Randomised trials	No limitations	Important inconsistency (-1)[1,]	No uncertainty	Imprecise or sparse data (-1)[3,]
Abstinence throughout follow-up (Beswick2003)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Abstinent in past month at follow-up (Beswick2003)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Left study early due to withdrawal (Umbricht1999)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Relapsed at follow-up (Gerra2000)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Concordance with naltrexone maintenance at 3-month follow-up (Gerra2000)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]
Self-rated withdrawal severity: Peak (Gerra1995, O'Connor1997. Better indicated by: lower scores)					
2	Randomised trials	No limitations	Important inconsistency (-1)[1]	No uncertainty	Imprecise or sparse data (-1)[3]
Self-rated withdrawal severity: Mean (O'Connor1997, Umbricht1999. Better indicated by: lower scores)					
2	Randomised trials	No limitations	Important inconsistency (-1)[1,]	No uncertainty	Imprecise or sparse data (-1)[3,]
Abstinent at 6-month follow-up (Gerra 2000)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[2,]

Summary of findings

Outcome	No of patients		Effect		Quality
	Opiate antagonist-accelerated detoxification	No opioid antagonists	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	135/173 (78%)	124/162 (76.5%)	RR 1.01 (0.90 to 1.13)	-	⊕⊕◯◯ Low
Abstinence throughout follow-up	9/45 (20%)	4/46 (8.7%)	RR 2.30 (0.76 to 6.94)	-	⊕⊕⊕◯ Moderate
Abstinent in past month at follow-up	16/45 (35.6%)	12/46 (26.1%)	RR 1.36 (0.73 to 2.55)	-	⊕⊕⊕◯ Moderate
Left study early due to withdrawal	4/32 (12.5%)	2/28 (7.1%)	RR 1.75 (0.35 to 8.84)	-	⊕⊕⊕◯ Moderate
Relapsed at follow-up	15/32 (46.9%)	18/32 (56.2%)	RR 0.83 (0.52 to 1.35)	-	⊕⊕⊕◯ Moderate
Concordance with naltrexone maintenance at 3-month follow-up	24/32 (75%)	17/32 (53.1%)	RR 1.41 (0.96 to 2.07)	-	⊕⊕⊕◯ Moderate
Self-rated withdrawal severity: Peak	96	88	-	SMD 0.95 (-1.20 to 3.10)	⊕⊕◯◯ Low
Self-rated withdrawal severity: Mean	79	83	-	SMD 0.51 (-0.58 to 1.60)	⊕⊕◯◯ Low

Abstinent at 6-month follow-up	14/32 (43.8%)	17/32 (53.1%)	RR 0.82 (0.49 to 1.37)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. I^2 >= 0.5
2. Single study
3. CIs do not favour either intervention

Table A17-13. Ultra-rapid detoxification under general anaesthesia or heavy sedation versus detoxification under minimal sedation

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Started 50mg naltrexone maintenance dose (versus clonidine control) (Collins2005, Favrat2006, McGregor2002)					
3	Randomised trials	No limitations	Important inconsistency (-1)[2,3]	No uncertainty	Strong association (+1)[1]
Serious adverse events (Seoane1997, Collins2005, De Jong2005)					
3	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[1]
Completion of detoxification (McGregor2002, Krabbe2003, Collins2005, Favrat2006)					
4	Randomised trials	No limitations	Important inconsistency (-1)[2]	No uncertainty	Imprecise or sparse data (-1)[3]
Abstinence: opiate negative urinalysis, hair analysis or self-report (1 month followup) (Krabbe2003, De Jong2005)					
2	Randomised trials	No limitations	Important inconsistency (-1)[2]	No uncertainty	Imprecise or sparse data (-1)[3]
Abstinence: opiate negative urinalysis, hair analysis or self-report (3 month followup) (Krabbe2003, Collins2005, Favrat2006)					
3	Randomised trials	No limitations	No important inconsistency	No uncertainty	Strong association (+1)[1]
Abstinence: opiate negative urinalysis, hair analysis or self-report (6 months followup) (McGregor2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[4] Strong association (+1)[1]
Abstinence: opiate negative urinalysis, hair analysis or self-report (12 months followup) (McGregor2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[3,4]
Started 50mg naltrexone maintenance dose (versus naltrexone w/o anaesthesia) (De Jong2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[4]

Summary of findings

Outcome	No of patients		Effect		Quality
	Ultra-rapid detoxification under anaesthesia	Detoxification under minimal sedation	Relative (95% CI)	Absolute (95% CI)	
Started 50mg naltrexone maintenance dose (versus clonidine control)	75/122 (61.5%)	22/118 (18.6%)	RR 3.87 (1.03 to 14.54)	-	⊕⊕⊕⊕ High
Serious adverse events	17/322 (5.3%)	4/322 (1.2%)	RR 3.62 (1.36 to 9.61)	-	⊕⊕⊕⊕ High
Completion of detoxification	115/137 (83.9%)	72/133 (54.1%)	RR 1.67 (0.88 to 3.18)	-	⊕⊕◯◯ Low
Abstinence: opiate negative urinalysis, hair analysis or self-report (1-month followup)	101/152 (66.4%)	87/150 (58%)	RR 1.54 (0.66 to 3.59)	-	⊕⊕◯◯ Low
Abstinence: opiate negative urinalysis, hair analysis or self-report (3-month followup)	26/86 (30.2%)	12/83 (14.5%)	RR 2.08 (1.18 to 3.68)	-	⊕⊕⊕⊕ High
Abstinence: opiate negative urinalysis, hair analysis or self-report	11/51 (21.6%)	4/50 (8%)	RR 2.70 (0.92 to 7.91)	-	⊕⊕⊕⊕ High

(6-months followup)					
Abstinence: opiate negative urinalysis, hair analysis or self-report (12-months followup)	10/51 (19.6%)	7/50 (14%)	RR 1.4 (.58 to 3.39)	-	⨁⨁⨁◯ Moderate
Started 50mg naltrexone maintenance (versus naltrexone without anaesthesia)	123/137 (89.8%)	133/135 (98.5%)	RR 0.91 (0.86 to 0.97)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. Large effect (RR >=2)
2. Significant heterogeneity (I squared > 0.5)
3. CI do not favour either intervention
4. Single study

Table A17-14. Rapid detoxification under moderate sedation versus clonidine

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of treatment (Arnold-Reed2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1] Strong association (+1)[2]
Abstinence: opiate-negative urinalysis, hair analysis or self-report (1-month follow-up) (Arnold-Reed2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Started 50mg naltrexone maintenance (Arnold-Reed2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
100% concordance with naltrexone during 1-month follow-up (Arnold-Reed2005)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Withdrawal severity: mean (Arnold-Reed2005)					
1	Randomised trials	Serious limitations (-1)[3]	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Rapid detoxification under moderate sedation	Clonidine under minimal sedation	Relative (95% CI)	Absolute (95% CI)	
Completion of treatment	36/41 (87.8%)	11/39 (28.2%)	RR 3.11 (1.86 to 5.20)	-	⨁⨁⨁⨁ High

Appendix 17b: Evidence profile tables A17-15 to A17-18 (psychosocial interventions in opioid detoxification)

Psychosocial interventions **2**

Table A17-15. Detoxification plus contingency management versus control 2
Table A17-16. Detoxification plus family intervention versus control 4
Table A17-17. Detoxification plus social and network intervention versus control 5
Table A17-18. Detoxification plus individual drug counselling versus control 6

Psychosocial interventions

Table A17-15. Detoxification plus contingency management versus control

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Hall1979, Higgins1984, McCaul1984, Higgins1986, Bickel1997)					
5	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	None
Abstinence: opiate-negative urinalysis or self-report (endpoint) (McCaul1984, Higgins1986, Bickel1997, Katz2004)					
4	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	None
Abstinence: opiate-negative urinalyses for entire duration of detoxification (McCaul1984)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2]

Summary of findings

Outcome	No of patients		Effect		Quality
	Contingency management	Control	Relative (95% CI)	Absolute (95% CI)	
Completion	56/91 (61.5%)	36/94 (38.3%)	RR 1.60 (1.18 to 2.16)		⨁⨁⨁◯ Moderate
Abstinence: opiate-negative urinalysis or self-report (endpoint)	47/151 (31.1%)	24/145 (16.6%)	RR 1.86 (1.20 to 2.86)		⨁⨁⨁◯ Moderate

Abstinence: opiate-negative urinalyses for entire duration of detoxification	5/10 (50%)	0/10 (0%)	RR 11.00 (0.69 to 175.86)		⨁⨁◯◯ Low

Footnotes:

1. No UK studies
2. Single study

Table A17-16. Detoxification plus family intervention versus control

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Mortality (Yandoli2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]
Abstinence: opiate-negative urinalysis or self-report (endpoint) (Yandoli2002)					
1	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[1]

Summary of findings

Outcome	No of patients		Effect		Quality
	Family intervention	Control	Relative (95% CI)	Absolute (95% CI)	
Mortality	2/41 (4.9%)	0/40 (0%)	RR 4.88 (0.24 to 98.60)	-	⨁⨁⨁◯ Moderate
Abstinence: opiate-negative urinalysis or self-report (endpoint)	6/41 (14.6%)	3/40 (7.5%)	RR 1.95 (0.52 to 7.27)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. Single study

Table A17-17. Detoxification plus social and network intervention versus control

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Galanter2004 Follow up:)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2]
Abstinence: Opiate-negative urinalysis or self-report (endpoint) (Galanter2004 Follow up:)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2] Strong association (+1)[3]

Summary of findings

Outcome	No of patients		Effect		Quality
	Social network intervention	Control	Relative (95% CI)	Absolute (95% CI)	
Completion of detoxification	24/33 (72.7%)	26/33 (78.8%)	RR 0.92 (0.70 to 1.21)	-	⨁⨁◯◯ Low
Abstinence: Opiate-negative urinalysis or self-report (endpoint)	12/33 (36.4%)	6/33 (18.2%)	RR 2.00 (0.85 to 4.69)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. No UK studies
2. Single study
3. Large effect (RR >= 2)

Table A17-18. Detoxification plus individual drug counselling versus control

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Rawson1983)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2]
Abstinence: opiate-negative urinalysis or self-report (endpoint) (Rawson1983)					
1	Randomised trials	Serious limitations (-1)[3]	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2]
Relapse: drug-dependent or incarcerated (6-month follow-up) (Rawson1983)					
1	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[1]	Imprecise or sparse data (-1)[2]

Summary of findings

Outcome	No of patients		Effect		Quality
	Individual drug counselling	Control	Relative (95% CI)	Absolute (95% CI)	
Completion of detoxification	4/25 (16%)	3/25 (12%)	RR 1.33 (0.33 to 5.36)	-	⨁⨁◯◯ Low
Abstinence: opiate-negative urinalysis or self-report (endpoint)	15/25 (60%)	13/25 (52%)	RR 1.15 (0.70 to 1.89)	-	⨁◯◯◯ Very low
Relapse: drug-dependent	7/25 (28%)	12/25 (48%)	RR 0.58 (0.28 to 1.23)	-	⨁⨁◯◯ Low

or incarcerated (6-month follow-up)					

Footnotes:

1. Old study
2. Single study
3. Given low completion rate, high proportion of abstinence unlikely

Abstinence: opiate-negative urinalysis, hair analysis or self-report (1-month follow-up)	14/36 (38.9%)	6/20 (30%)	RR 1.30 (0.59 to 2.84)	-	⨁⨁⨁◯ Moderate
Started 50mg naltrexone maintenance	31/36 (86.1%)	10/20 (50%)	RR 1.72 (1.09 to 2.72)	-	⨁⨁⨁◯ Moderate
100% concordance with naltrexone over 1-month follow-up	20/36 (55.6%)	8/20 (40%)	RR 1.39 (0.75 to 2.56)	-	⨁⨁⨁◯ Moderate
Withdrawal severity: Mean	33	8	-	SMD -1.70 (-2.56 to -0.84)	⨁⨁◯◯ Low

Footnotes:

1. Single study
2. RR >= 2
3. Not intent-to-treat, with large dropout rate

Appendix 17c: Evidence profile tables A17-19 (treatment settings for opioid detoxification)

Settings **2**

Table A17-19. Inpatient versus community-based 2

Settings

Table A17-19. Inpatient versus community-based

Quality assessment

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Completion of detoxification (Wilson1975, Gossop1986, Day2006)					
3	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[1]	Strong association (+1)[2]

Summary of findings

Outcome	No of patients		Effect		Quality
	Inpatient Setting	Outpatient Setting	Relative (95% CI)	Absolute (95% CI)	
Completion of detoxification	50/78 (64.1%)	28/93 (30.1%)	RR 2.19 (1.12 to 4.29)	-	⨁⨁⨁◯ Moderate

Footnotes:

1. Very old studies
2. Large effect (RR >= 2)

10. GLOSSARY

12-step group: A non-profit fellowship of people who meet regularly to help each other remain abstinent. The core of the 12-step programme is a series of 12 stages that include admitting to a drug problem, seeking help, self-appraisal, confidential self-disclosure, making amends (when possible) where harm has been done, achieving a spiritual awakening and supporting other people who misuse drugs who want to recover.

Abstinence: Abstinence-oriented treatments aim to reduce an individual's level of drug use, with the ultimate goal of refraining from use altogether.

Agonist: An agonist is a substance that mimics the actions of a **neurotransmitter** or hormone to produce a response when it binds to a specific receptor in the brain. **Opioid** drugs, for example heroin and **methadone**, are agonists that produce responses such as 'liking', analgesia and respiratory depression.

Alpha$_2$ adrenergic agonist: An adrenergic **agonist** has an adrenaline-like action upon adrenergic receptors in the brain. Stimulation of the alpha adrenergic receptors leads to constriction of the bronchi and blood vessels, and dilation of the pupils of the eyes. Consequently, alpha$_2$ adrenergic agonists are useful in improving **opioid withdrawal symptoms** associated with the **noradrenaline system**, including sweating, shivering, and runny nose and eyes. Clonidine and lofexidine are examples of adrenergic agonists used as adjunctive medication in opioid detoxification.

Antagonist: In contrast to the action of an **agonist**, an antagonist, such as **naltrexone**, binds to a specific receptor in the brain but does not activate it. Therefore, if an agonist, for example heroin or **methadone**, is present and activating the receptor, taking naltrexone will counteract the activation, resulting in withdrawal.

Buprenorphine: An analgesic **opioid** substitute used in **maintenance**-oriented treatment, buprenorphine has both **agonist** and **antagonist** properties.

Cannabis: Cannabis is a generic term denoting the various psychoactive preparations of the hemp plant, including marijuana leaves, hashish resin and oil (WHO, 2006). It is the most commonly used illicit drug in the UK.

Cognitive behavioural therapy (CBT): Cognitive behavioural therapy encompasses a range of behavioural and cognitive behavioural therapies, in part derived from the cognitive behavioural model of affective disorders, in which the patient works collaboratively with a therapist using a shared formulation to achieve specific treatment goals. Such goals may include recognising the impact of behavioural and/or thinking patterns on feeling states and encouraging alternative cognitive and/or behavioural

coping skills to reduce the severity of target symptoms and problems. Therapies relevant to the field of drug misuse include **standard cognitive behavioural therapy** and **relapse-prevention cognitive behavioural therapy**.

Community reinforcement approach: In community reinforcement, emphasis is placed on environmental contingencies in aspects of life such as work, recreation, family involvement, and so on, to promote a lifestyle that is more rewarding than drug misuse (Roozen *et al.*, 2004).

Confidence interval (CI): The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)

Contingency management (CM): Contingency management provides a system of incentives and disincentives designed to make continual drug use less attractive and abstinence more attractive (Griffith *et al.*, 2000). The three main methods of providing incentives are voucher-based, whereby vouchers representing monetary values are provided upon receipt of biological samples (usually urine) that are negative for the tested drugs, prize-based (whereby participants receive prize-draw entries upon presentation of a negative biological sample) and privilege-based (whereby participants receive privileges such as take home methadone doses upon presentation of a negative biological sample).

Deep/heavy sedation: A high level of sedation, where the subject may not be easily aroused or purposefully respond to verbal commands and may only respond minimally to very significant stimuli (such as high levels of pain). He or she may experience partial or complete loss of protective reflexes, including the ability to independently and continuously maintain an open airway. The individual may therefore require assistance in maintaining an open airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Dependence: Dependence is defined by the WHO as a strong desire or sense of compulsion to take a substance, a difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others (WHO, 2006).

Detoxification: Detoxification is the process by which an individual is withdrawn from the effects of a psychoactive substance. As a clinical procedure, the withdrawal process should be supervised and carried out in a safe and effective manner, such that withdrawal symptoms are minimised. Typically, the individual is clinically intoxicated or already in withdrawal at the outset of detoxification. Detoxification may involve the administration of medication, the dose of which is calculated to relieve withdrawal symptoms without inducing intoxication, and is gradually tapered off as the individual recovers.

Drug misuse/problem drug use: Drug misuse is the use of a substance for a purpose not consistent with legal or medical guidelines (WHO, 2006). The ACMD defines problem drug use as a condition that may cause an individual to experience social, psychological, physical or legal problems related to intoxication and/or regular excessive consumption, and/or dependence; any injection drug use also constitutes misuse (ACMD, 1998).

False negative: A test result that fails to detect an effect, condition or drug when it is in fact present.

False positive: A test result that incorrectly shows an effect, condition or drug to be present when it is not.

Family intervention: A psychological intervention derived from a model of the interactional processes in families. Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of drug misuse. Additionally, the aim is to change the nature of the interactions so that they may develop relationships that are more supportive and have less conflict (NICE, 2004).

General anaesthesia: Under general anaesthesia, an individual is unconscious and unresponsive, even in the face of significant stimuli. The ability to independently maintain ventilatory function is often impaired and assistance is frequently required in maintaining an open airway. Cardiovascular function may be impaired.

Harm reduction: Measures aiming to prevent or reduce negative health or other consequences associated with drug misuse, whether to the drug-using individual or to society. Attempts are not necessarily made to reduce the drug use itself.

Incremental cost-effectiveness ratio (ICER): The difference in the mean costs in the population of interest divided by the differences in the main outcomes in the population of interest.

Individual drug counselling: The assessment of an individual's needs, provision of information and referral to services to meet these needs (including psychosocial interventions, methadone and residential rehabilitation). No attempt is made to engage in any specific formal psychological intervention. Sessions are normally weekly and last 15–20 minutes (Rawson *et al.*, 1983). This to some extent resembles keyworking as used in the UK drug treatment field.

Interpersonal therapy (IPT): A discrete, time-limited, structured psychological intervention that focuses on interpersonal issues and where therapist and service user: a) work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current drug misuse, feelings states and/or problems; and b) seek to reduce

drug misuse problems by learning to cope with or resolve interpersonal problem areas (Weissman *et al.*, 2000).

Legally coerced (drug) treatment: This requires that the person who misuses drugs enter into treatment as an alternative or adjunct to criminal sanctions (Wild *et al.*, 2002). Such treatment can either be legally ordered by the court or through diversion away from the judicial process, usually following arrest and charge for drug-related and other offences.

Lofexidine: An **alpha$_2$ adrenergic agonist** currently licensed and used widely in the UK to ameliorate a cluster of **opioid withdrawal symptoms** (those associated with the **noradrenaline system**, including sweating, shivering, and runny nose and eyes).

Maintenance: In the UK context this refers primarily to the pharmacological maintenance of people who are **opioid** dependent; that is, prescription of opioid substitutes (**methadone** or **buprenorphine**). This aims to reduce illicit drug use and its consequent harms.

Meta-analysis: The use of statistical techniques to integrate the results of several independent studies.

Metabolite: A chemical product derived from breakdown (metabolism) of another chemical.

Methadone: A synthetic, psychoactive **opioid** substitute used in **maintenance**-oriented treatment, particularly heroin dependence. Methadone has **agonist** properties.

Minimal/light sedation: This involves the administration of medication in order to deal with anxiety, insomnia or agitation. The defining characteristic of this type of sedation is that the individual still appears relatively awake and is able to communicate clearly at all times. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation: This occurs where the individual appears obviously sedated but, importantly, is able to independently maintain an open airway and respond to stimuli purposefully (such as verbal questioning).

Naloxone: A short-acting **antagonist** that blocks the effects of **opioid** drugs on receptors in the brain, naloxone is used to detect the presence of opioid effects (in what is known as a naloxone challenge test) and also in emergency situations to reverse opioid overdose.

Naltrexone: An **antagonist** that blocks the effects of **opioid** drugs on receptors in the brain, naltrexone is used in **maintenance** treatment to prevent detoxified service users from relapsing to opioid use.

National Collaborating Centre for Mental Health (NCCMH): One of seven centres established by the **National Institute for Health and Clinical Excellence (NICE)** to develop guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England and Wales. Established in 2001, the NCCMH is responsible for developing mental health guidelines, and is a partnership between the Royal College of Psychiatrists and the British Psychological Society.

National Institute for Health and Clinical Excellence (NICE): An independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. It provides guidance on three areas of health: clinical practice, public health and health technologies.

National Treatment Agency for Substance Misuse (NTA): The NTA is a special health authority, which was established by the government in 2001. It is tasked with increasing the availability, capacity and effectiveness of treatment for drug misuse in England and embraces user involvement as a core component of its strategy.

Near-patient testing: This refers to the process of obtaining a biological sample from a service user and using a drug-testing kit to immediately detect the presence of any of a variety of substances (for example, **opioids**, amphetamines, cocaine metabolite, benzodiazepines, methadone and cannabis) on site. This process eliminates the need for external laboratory support and provides rapid results.

Needle and syringe exchange: A service aiming to reduce transmission of blood-borne viruses through the promotion of safer drug injection behaviour, primarily via the distribution of sterile needles, but often also by offering education and other psychosocial interventions.

Neurotransmitter: A chemical messenger (for example, dopamine or **noradrenaline**) used by nerve cells to transmit nerve impulses from one nerve cell (neuron) to another, or between neurons and other tissues, such as muscles or glands.

Noradrenaline system: A neuronal system that is responsible for the synthesis, storage and release of the neurotransmitter noradrenaline, which exists in both the central and peripheral nervous systems. It is the primary neurotransmitter released by the sympathetic nervous system, which mediates the 'fight or flight' reaction, preparing the body for action by affecting cardiovascular function, gastrointestinal motility and secretion, bronchiole dilation, glucose metabolism, and so on.

Odds ratio (OR): A measure of the relative benefit of the experimental treatment that can be obtained by dividing the experimental odds by the control odds.

Opioid: A class of psychoactive substances derived from the poppy plant, including opium, morphine and codeine, as well as their semi-synthetic counterparts, including heroin (WHO, 2004). In this guideline, the term 'opioid' is used more broadly to

incorporate synthetic compounds (including **methadone**) with similar properties, also commonly known as opioids.

Psychosocial intervention: Any formal, structured psychological or social intervention with assessment, clearly defined treatment plans and treatment goals, and regular reviews (NTA, 2006), as opposed to advice and information, drop-in support or informal keyworking.

Quality adjusted life years (QALY): A form of utility measure calculated by estimating the total life years gained from a treatment and weighting each year with a quality-of-life score in that year.

Randomised controlled trial (RCT): An experiment in which investigators randomly allocate eligible people into groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the different groups. Through randomisation, the groups should be similar in all aspects, apart from the treatment they receive during the study.

Rapid/ultra-rapid detoxification: Approaches for detoxifying those dependent upon **opioids** whereby opioid **antagonists**, such as **naloxone**, **naltrexone** or nalmefene, are used under **general anaesthesia** or **deep sedation**. The aim is to flood the brain with an opioid antagonist to remove all agonists while the sedation (for rapid detoxification) or anaesthesia (ultra-rapid detoxification) minimises discomfort. The individual is then maintained on naltrexone.

Relapse-prevention cognitive behavioural therapy: This differs from **standard cognitive behavioural therapy** in the emphasis on training drug users to develop skills to identify situations or states where they are most vulnerable to drug use, to avoid high-risk situations, and to use a range of cognitive and behavioural strategies to cope effectively with these situations (Carroll & Onken, 2005).

Relative risk (RR): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Residential rehabilitation programme: Residential rehabilitation centres provide accommodation in a drug-free environment and a range of structured interventions to address drug misuse, including, but not limited to, abstinence-oriented interventions (NTA, 2006). Services vary and are based on a number of different treatment philosophies.

Screening: The systematic application of a test or enquiry to identify individuals at high risk of developing a specific disorder who may benefit from further investigation

or preventative action (Peckham & Dezateux, 1998). Routine screening for drug misuse in the UK is largely restricted to criminal justice settings, including police custody and prisons (Matrix Research and Consultancy & NACRO, 2004).

Self-help group: A group of people who misuse drugs meet regularly to provide help and support for one another. The group is typically community-based, peer-led and non-professional.

Sensitivity: A term used to assess **screening** tools, sensitivity refers to the proportion of people with disease who test positive for that disease.

Short-term psychodynamic intervention: A psychological intervention, derived from a psychodynamic/psychoanalytic model in which: a) therapist and service user explore and gain insight into conflicts and how these are represented in current situations and relationships, including the therapy relationship; b) service users are given an opportunity to explore feelings and conscious and unconscious conflicts originating in the past, with the technical focus on interpreting and working through conflicts; c) therapy is non-directive and service users are not taught specific skills such as thought monitoring, re-evaluation or problem solving. Treatment typically consists of 16–30 sessions (Leichsenring *et al.*, 2004).

Social network interventions: Professionals seek to promote change by helping the person who misuses drugs to engage with a close network of family members or friends who provide positive social support for attempting or maintaining abstinence (Copello *et al.*, 2005).

Specificity: A term used to assess **screening** tools, specificity refers to the proportion of people without disease who test negative for that disease.

Standard cognitive behavioural therapy: A discrete, time-limited, structured psychological intervention, derived from a cognitive model of drug misuse (Beck *et al.*, 1993). There is an emphasis on identifying and modifying irrational thoughts, managing negative mood and intervening after a lapse to prevent a full-blown relapse (Maude-Griffin *et al.*, 1998).

Standard deviation (SD): A statistical measure of variability in a population of individuals or in a set of data. While the average measures the expected middle position of a group of numbers, the standard deviation is a way of expressing how different the numbers are from the average. The standard deviation is (approximately) the amount by which the average person's score differs from the average of all scores.

Standardised mean difference (SMD): In a **meta-analysis**, a way of combining the results of studies that may have measured the same outcome in different ways, using different scales. Statistically, it is calculated by dividing the weighted average effect size by the pooled standard deviation. The SMD is expressed as a standard value with no units.

Stimulant: Broadly any substances that activate, enhance or increase neural activity (WHO, 2006). Illicit stimulants include cocaine, crack cocaine and methamphetamine. Cocaine is one of the most commonly misused stimulants in the UK; crack cocaine refers to the cocaine alkaloid that has been purified from the other components of cocaine powder, and methamphetamine is one of a group of synthetic substances (amphetamines) with broadly similar properties to cocaine.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined 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**.

Tramadol: A synthetic **opioid**, tramadol is a weak **agonist** which may also have partial **antagonist** properties. More commonly used in the context of pain relief, it is neither licensed nor routinely used in the UK for the treatment of opioid dependence.

Weighted mean difference (WMD): A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study (for example, how much influence each study has on the overall results of the **meta-analysis**) is determined by the precision of its estimate of effect and, in the statistical software used by the **NCCMH**, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

Withdrawal symptoms: Withdrawal symptoms ensue when a person who has become tolerant to the effects of a drug stops taking it. Such symptoms typically emerge within 6–12 hours for short-acting **opioids** such as heroin and about 24–36 hours after the last dose of methadone or buprenorphine, depending on the dose. Withdrawal can also ensue when an opioid **antagonist**, such as **naloxone** or **naltrexone** is taken; this is called precipitated or abrupt withdrawal. Opioid withdrawal symptoms can include pupil dilation, diarrhoea, low mood, irritability, anxiety, insomnia, muscular and abdominal pains, restlessness and 'craving'. In addition, tachycardia, sweating, runny nose, hair standing on end and shivering are generally experienced.

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12. ABBREVIATIONS

ACMD	Advisory Council on the Misuse of Drugs
AE	adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AIDS	autoimmune deficiency syndrome
AMED	A bibliographic database produced by the Health Care Information Service of the British Library
APA	American Psychiatric Association
ASI	Addiction Severity Index
CA	Cost analysis
CBA	Cost-benefit analysis
CBT	cognitive behavioural therapy
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	Cost-minimisation analysis
COWS	Clinical Opiate Withdrawal Scale
CSAT	Center for Substance Abuse Treatment
CUA	Cost-utility analysis
DD	drug dependence
DDU	drug-dependence unit
DH	Department of Health
DIP	Drug Interventions Programme
DSM	Diagnostic and Statistical Manual of Mental Disorders (versions III-R and IV-TR)
DTTO	Drug Treatment and Testing Order
EMBASE	Excerpta Medica database
EEG	electroencephalogram
F	the statistic calculated by analysis of variance (F ratio)
GDG	Guideline Development Group
GFN	guanfacine
GP	general practitioner
GRADE	Grading of Recommendations: Assessment, Development and Evaluation (Working Group)
GRP	Guideline Review Panel

HIV	human immunodeficiency virus
HMIC	Health management and policy database from the Healthcare Management Information Consortium
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
K	number of studies
LAAM	levo-alpha acetyl methadol
LDQ	Leeds Dependence Questionnaire
LSD	lysergic acid diethylamide
MAP	Maudsley Addiction Profile
MEDLINE	Compiled by the US National Library of Medicine and published on the web by Community of Science, MEDLINE is a source of life sciences and biomedical bibliographic information
MMT	methadone maintenance treatment
n	number of participants in a group
N	total number of participants
NACB	National Academy of Clinical Biochemistry
NACRO	National Association for the Care and Rehabilitation of Offenders
NCCMH	National Collaborating Centre for Mental Health
NDTMS	National Drug Treatment Monitoring System
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NIDA	National Institute on Drug Abuse
NSF	National Service Framework
NTA	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcomes Research Study
OHE HEED	Office of Health Economics, Health Economics Evaluation Database
OR	odds ratio
OTI	Opiate Treatment Index
OWS	Opiate Withdrawal Scale
p	probability
PICO	patient, intervention, comparison and outcome
PILOTS	An electronic index to the worldwide literature on post-traumatic stress disorder and other mental-health

	consequences of exposure to traumatic events, produced by the US National Center for PTSD
PSS	Personal Social Services
PsycINFO	An abstract (not full text) database of psychological literature from the 1800s to the present
QALY	quality adjusted life year
qid	four times a day
r	correlation
RCT	randomised controlled trial
RD	rapid detoxification (-GA, with general anaesthesia)
RODA	rapid opioid detoxification under anaesthetic
RODS	rapid opioid detoxification under sedation
RR	relative risk
SCAN	Specialist Clinical Addiction Network
SDS	Severity of Dependence Scale
SIGLE	System for Information on Grey Literature in Europe database
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardised mean difference
SODQ	Severity of Opiate Dependence Questionnaire
t	t-statistic
tid	three times a day
WHO	World Health Organization
WMD	weighted mean difference
χ	chi

The guideline on *Drug misuse: opioid detoxification*, commissioned by NICE and developed by the National Collaborating Centre for Mental Health, sets out clear, evidence-based recommendations for healthcare staff on how to work with people who misuse opioids to significantly improve their treatment and care, and to deliver detoxification safely and effectively. Of the estimated 4 million people in the UK who use illicit drugs each year, approximately 50,000 misuse opioids (such as heroin, opium, morphine, codeine and methadone). Opioid misuse presents a considerable health risk and can lead to significant social problems. This NICE guideline is an important tool in helping people to overcome their drug problem.

This publication brings together all of the evidence that led to the recommendations in the NICE guideline. It provides an overview of drug misuse and opioid detoxification and covers assessment and testing, pharmacological and physical interventions used in detoxification, psychosocial interventions to support detoxification, and the settings in which the treatment can take place. The book is illustrated by the experiences of people who have been dependent on opioids, and there is also advice for family members and carers of people with a drug problem.

An accompanying CD contains further information about the evidence, including

- included and excluded studies;
- profile tables that summarise both the quality of the evidence and the results of the evidence synthesis;
- all meta-analytical data presented as forest plots; and
- detailed information about how to use and interpret forest plots.

This book is accompanied by another guideline,
Drug misuse: psychosocial interventions.

Cover photo: Ryan Li

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ISBN 978-1-85433-469-5